The American Journal of Medicine

February 1953

The American Journal of Medicine

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, N. Y. Yearly Subscription, $12.00 U. S. A., $13.00 Canada and Latin American countries; $15.00 Foreign. Single Numbers $2.00: Symposia Numbers $4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. February, 1953—Volume XIV, No. 2. Copyright, 1953, by The American Journal of Medicine, Inc.

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

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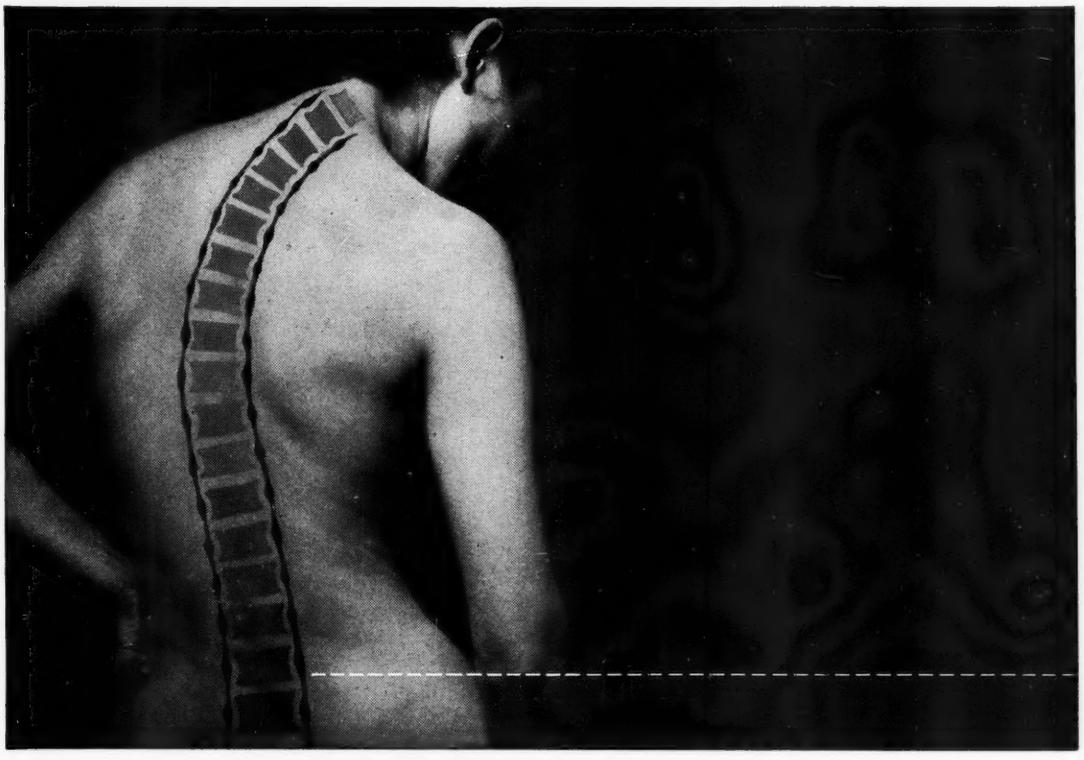

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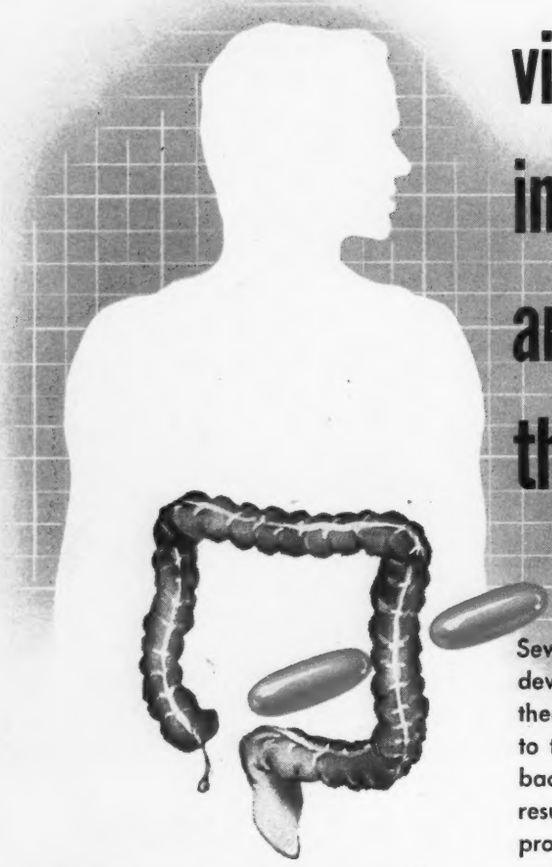

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1. Gewin, H. M., and Friou, G. J.: *Yale Jour. Biol. & Med.*, 23:332, Feb., 1951.

2. Marshall, H. C., Jr., Palmer, W. L., and Kirsner, J. B.: J.A.M.A., 144:900, Nov. 11, 1950.

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The American Journal of Medicine

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Editorial

Clinical Studies

Many papers dealing with the treatment of hypertension report inadequately controlled observations in too small a number of patients studied for too short a time to permit of even the most tentative conclusions. The present paper is one of the exceptions, representing an extensive, painstaking and reasonably well controlled effort to determine the clinical usefulness of Dibenzyline and related adrenergic blocking agents as hypotensogenic drugs, evaluated in a forthright manner. As a practical method of treatment, Dibenzyline is of limited value but the results certainly justify continued effort along these lines.

Of the available hypotensive agents, 1-hydrazinophthalazine is one of the more promising. The present study on sixty-five patients with hypertension of various etiologies indicates a significant response in blood pressure and symptomatology in a number of patients with essential hypertension. Obviously, relatively short periods of observation leave many crucial points unanswered but it is clear that encouraging progress in the management of hypertension is being made.

An important consideration in the use of hypotensive agents in the management of essential hypertension is the effect on renal hemodynamics, which may be adversely affected. In the case of Veriloid, most patients responded with a fall in GFR and a rise in ERPF, with resultant reduction in the filtration fraction, indicating reduced resistance of the renal arterioles; in patients with more marked initial hypertension, however, the findings indicate further increase in efferent arteriolar constriction.

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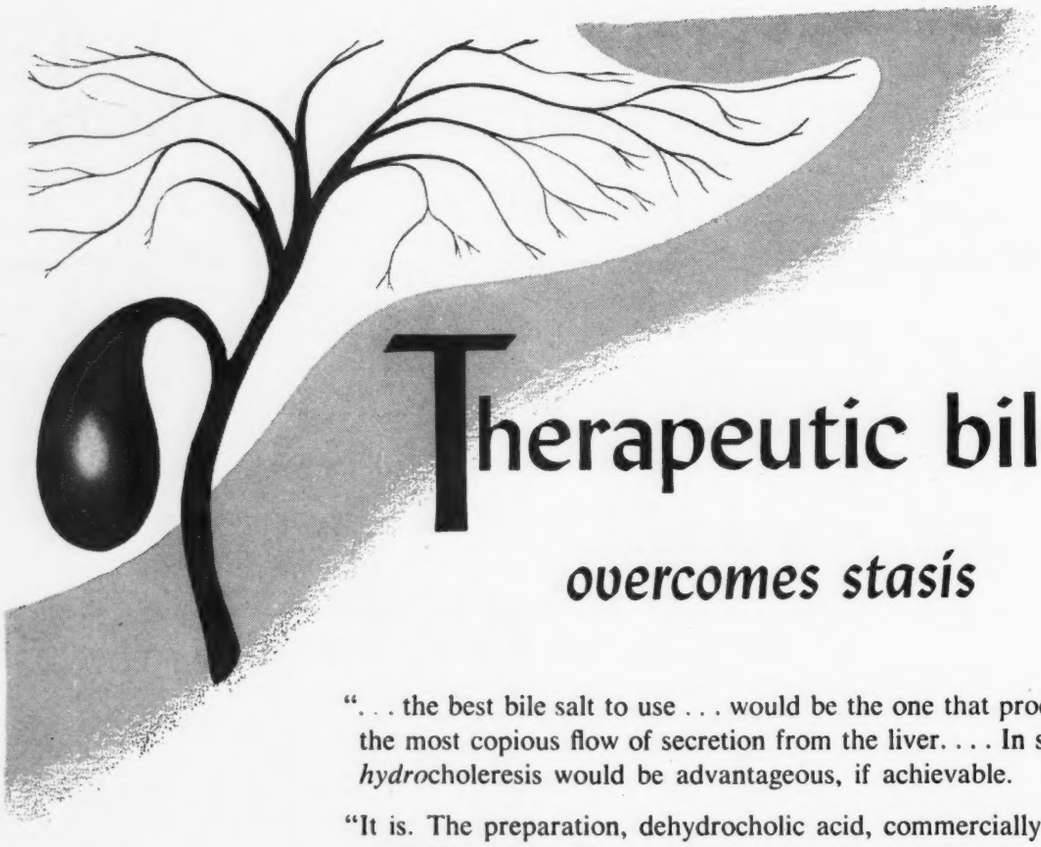

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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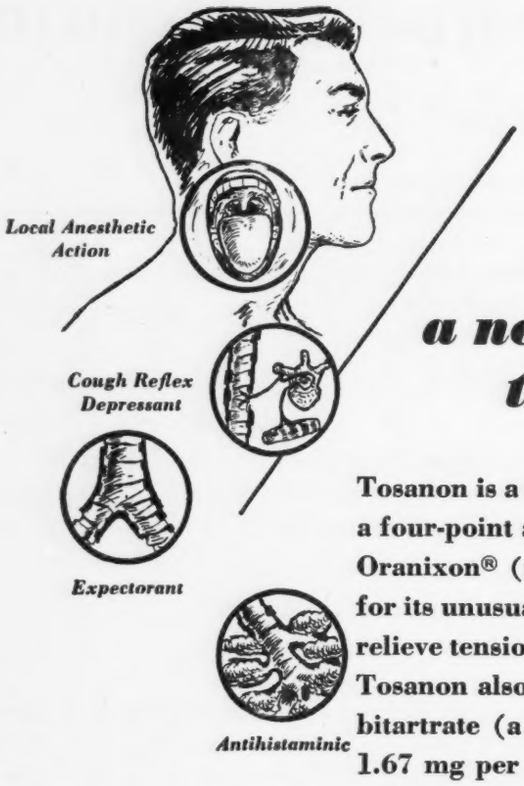

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Harding, F. E.: West. J. Surg. **52**:31 (Jan.) 1944.

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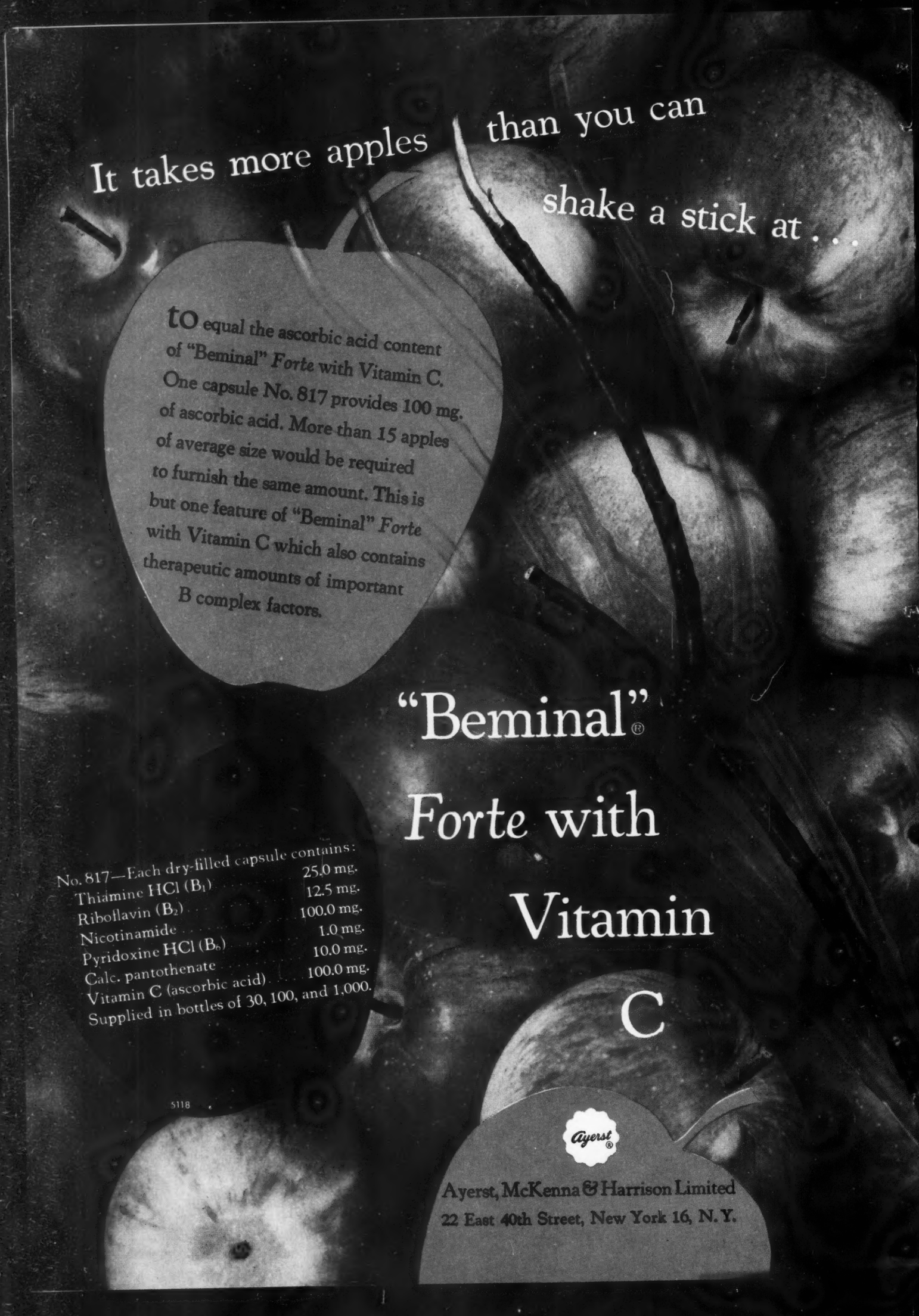
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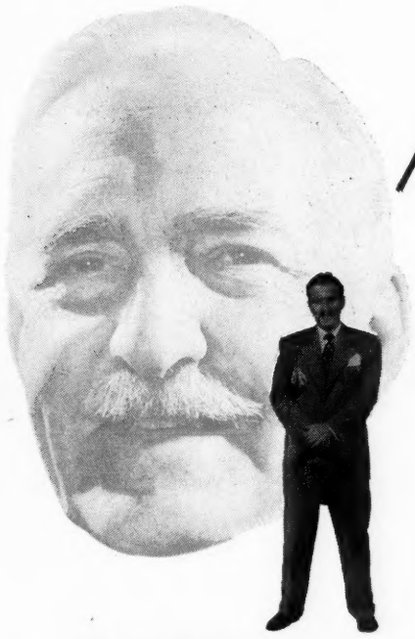

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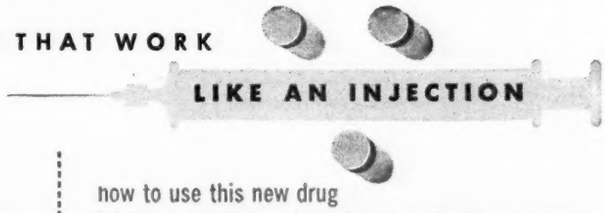

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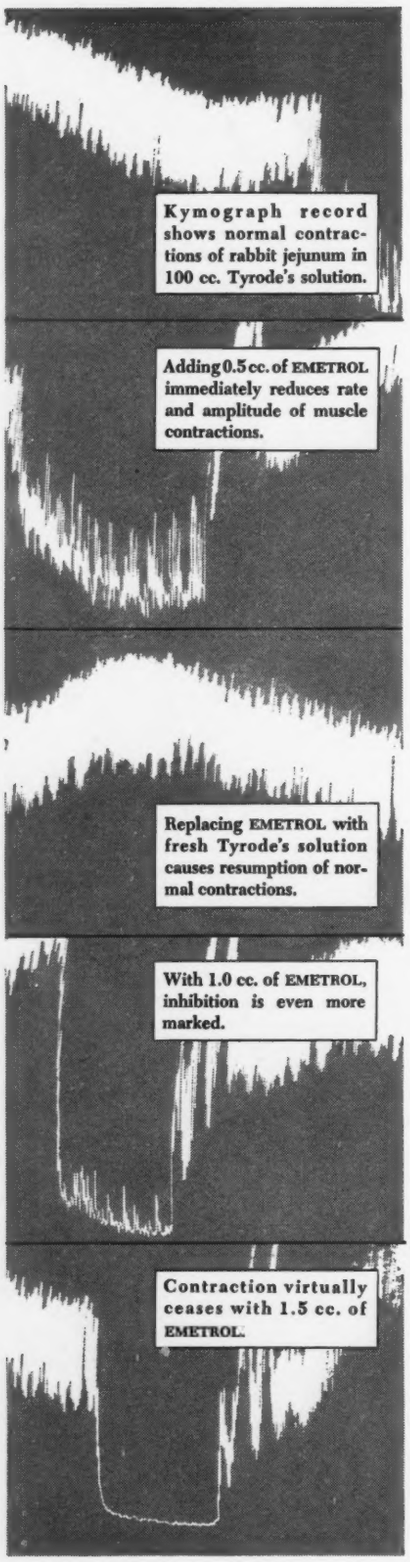

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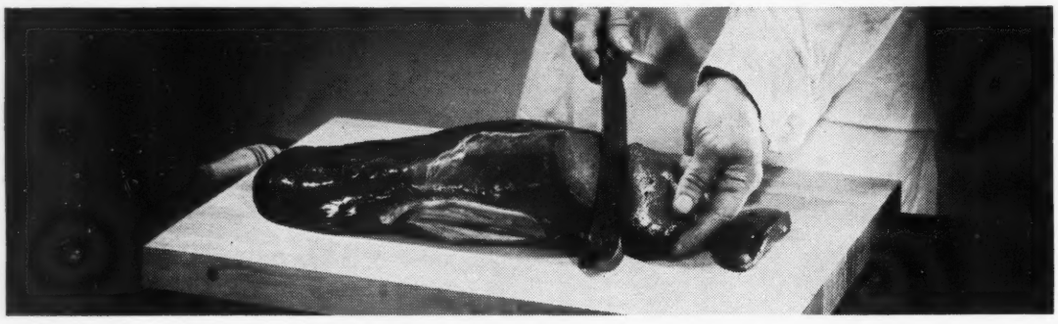
1. Spies, T.: International Conference on Vitamins and Hormones, Havana, Cuba, 1952.
2. Chow, B.F.: Southern Med. J., *45*:604, 1952.
3. Conley, C.L., Green, T.W., Hartman, R.C. and Krevans, J.R.: Am. J. Med., *13*:284, 1952.
4. Campbell, R.R. and Pruitt, F.W.: Am. J. Med. Sci., *224*:252, 1952.

"...The most potent



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***1. Barrett, R. H., *The Analeptic Effect of Sodium Succinate on Barbiturate Depression in Man.* Current Researches in Anesthesia and Analgesia. 26: pages 74-81 and 105-113, March-April, May-June, 1947.**

2. Greenfield, Irving, *Sodium Succinate as a Test of Circulatory Efficiency.* Ann. Int. Med. 32: 524-527, March 1950.

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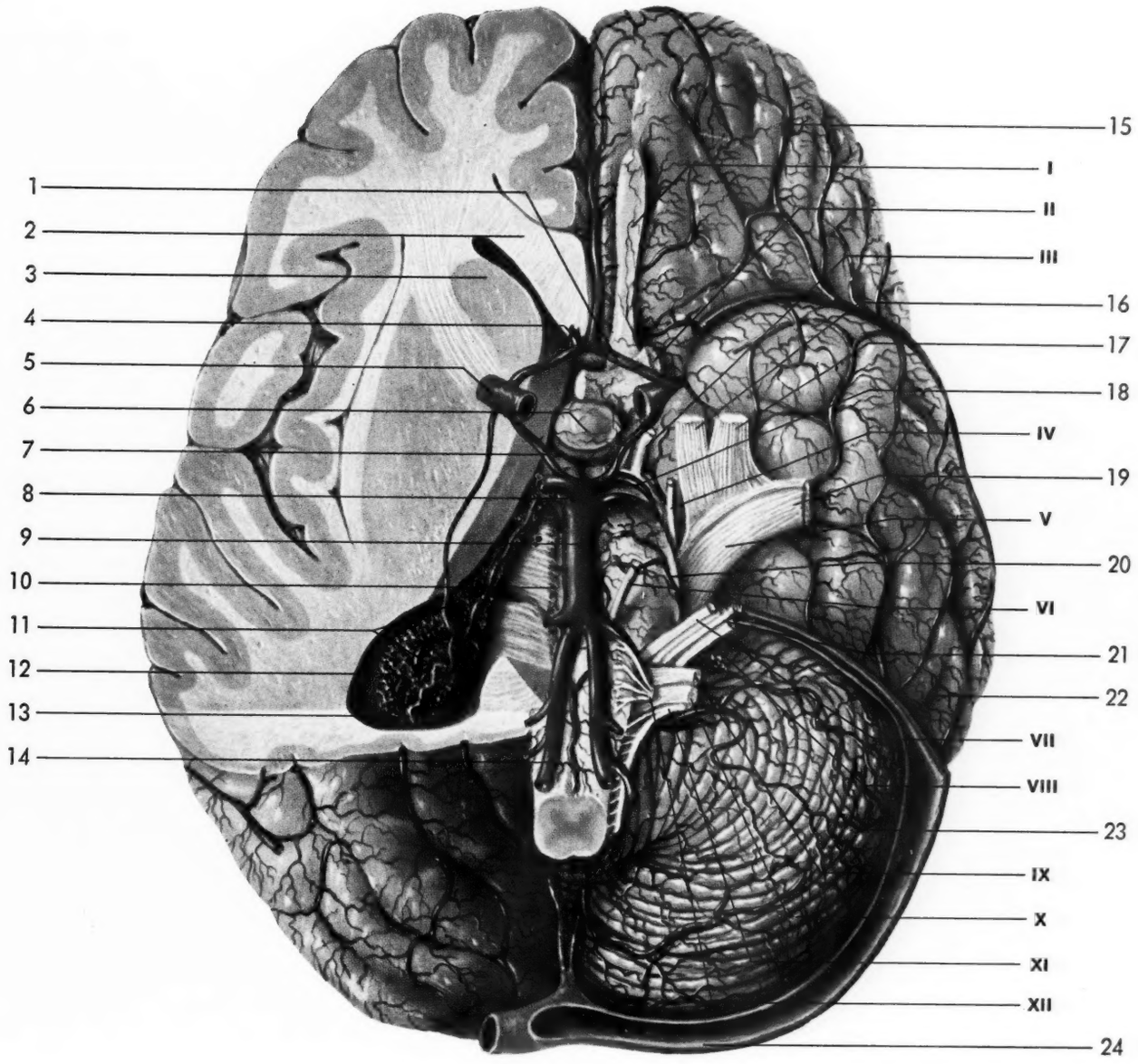

1. Anterior cerebral artery
2. Trunk of corpus callosum
3. Head of caudate nucleus
4. Anterior communicating artery
5. Middle cerebral artery
6. Hypophysis
7. Posterior communicating artery
8. Superior cerebellar artery
9. Basilar artery
10. Internal cerebral vein
11. Choroid artery and vein
12. Choroid plexus of lateral ventricle
13. Inferior cornu of lateral ventricle
14. Vertebral artery
15. Frontal lobe
16. Ophthalmic nerve
17. Maxillary nerve
18. Posterior cerebral artery
19. Mandibular nerve
20. Pons
21. Intermediate nerve
22. Temporal lobe
23. Cerebellum
24. Left transverse sinus

CRANIAL NERVES

I. Olfactory nerve
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IV. Trochlear nerve
V. Trigeminal nerve
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VIII. Acoustic nerve
IX. Glossopharyngeal nerve
X. Vagus nerve
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XII. Hypoglossal nerve

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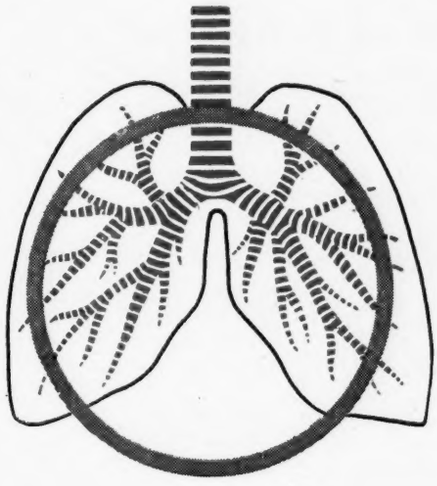
—*an Effective Treatment*



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(1) Bordley, J. E., et al.: Bull. Johns Hopkins Hosp. 85: 396, 1949; (2) Rose, B., et al.: Canad. M. A. J. 62: 6, 1950; (3) Randolph, T. G., and Rollins, J. P.: In Proceedings of First Clinical ACTH Conference, edited by J. R. Mote. Philadelphia, The Blakiston Co., 1950, p. 479; (4) McCombs, R. P., et al.: Bull. New England M. Center 12: 187, 1950; (5) Baldwin, H. S., and DeGara, P. F.: J. Allergy 23: 15, 1952; (6) McCombs, R. P.: New England J. Med. 247: 1, 1952.

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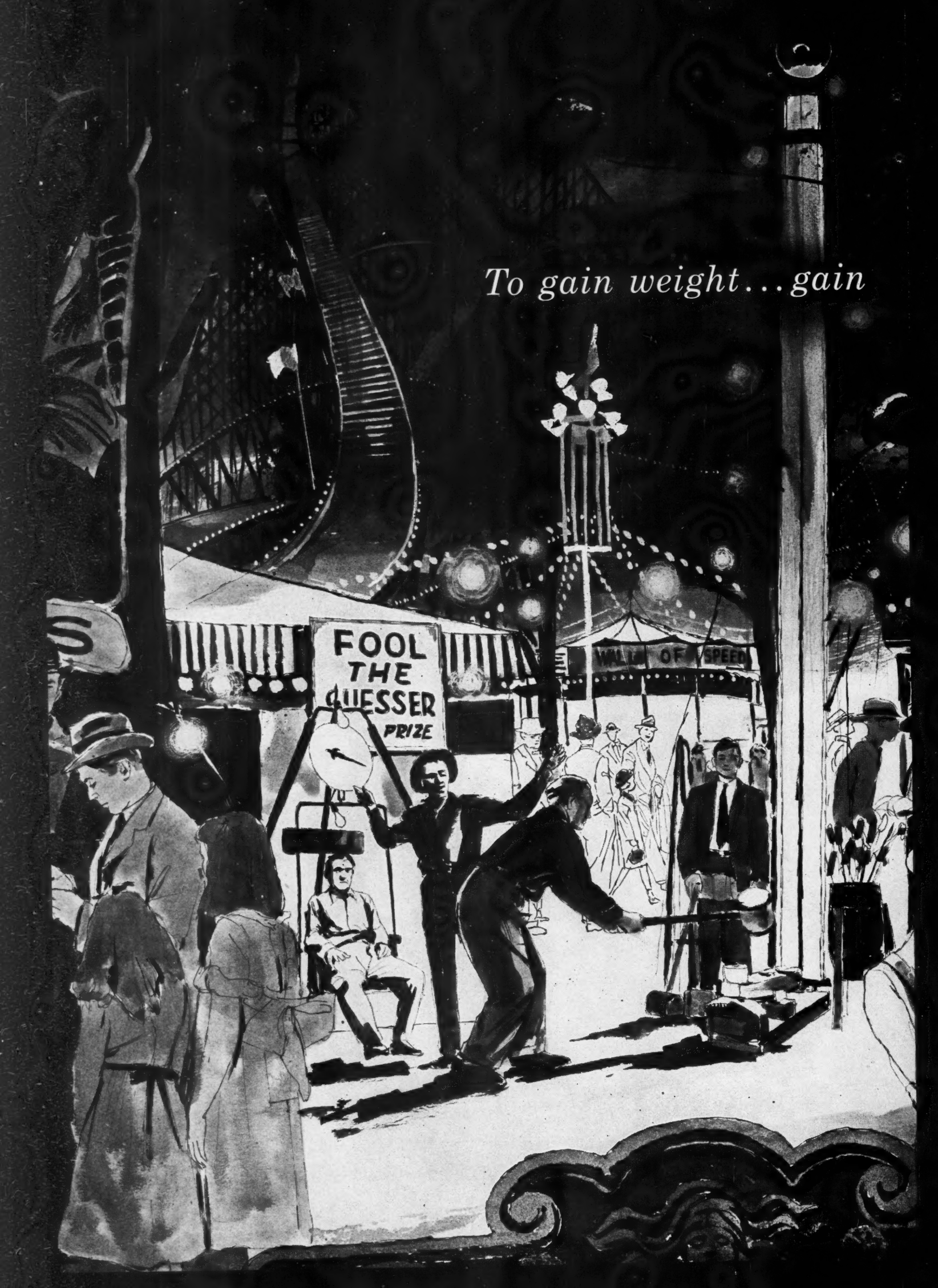
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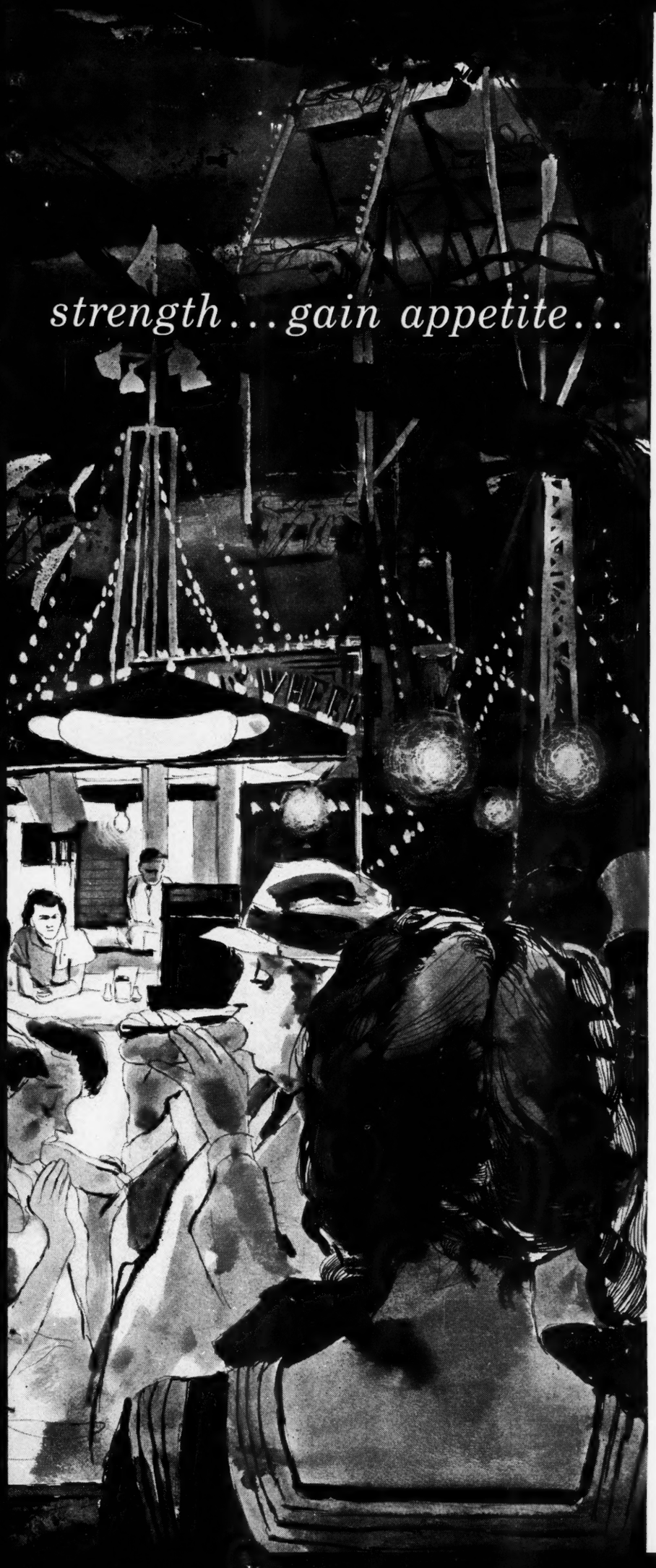

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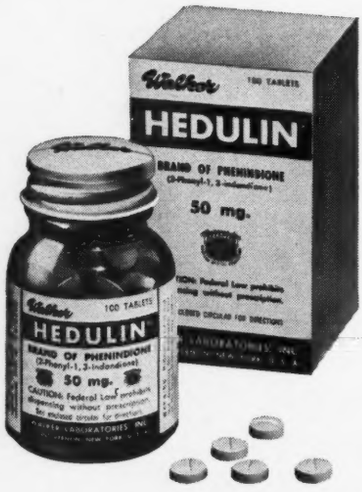

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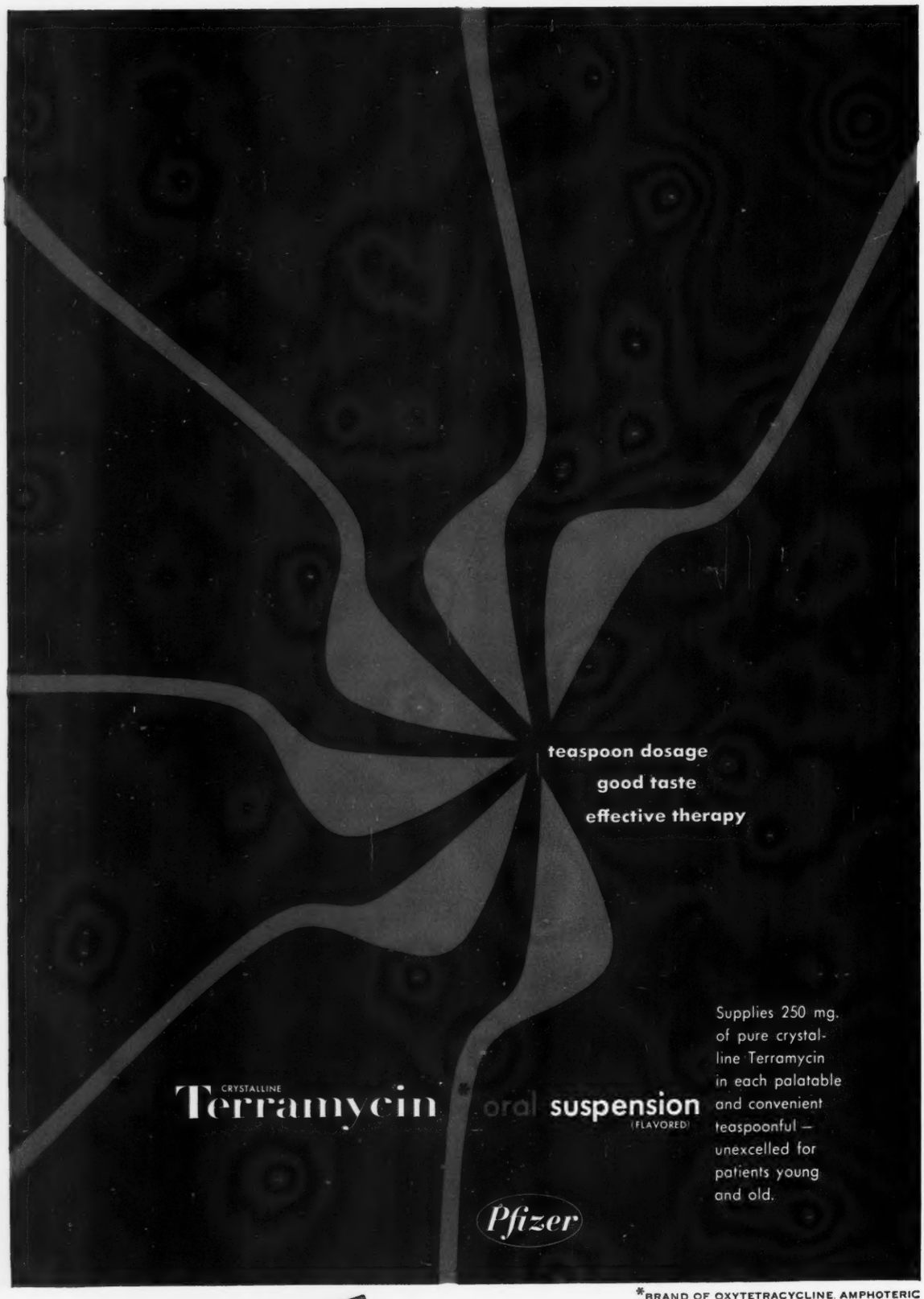

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*Cass, L. J. and Frederik, W. S.: Am. Pract. and Digest of Treat., 2:844, 1951. Report of blind test on 52 hospitalized patients.

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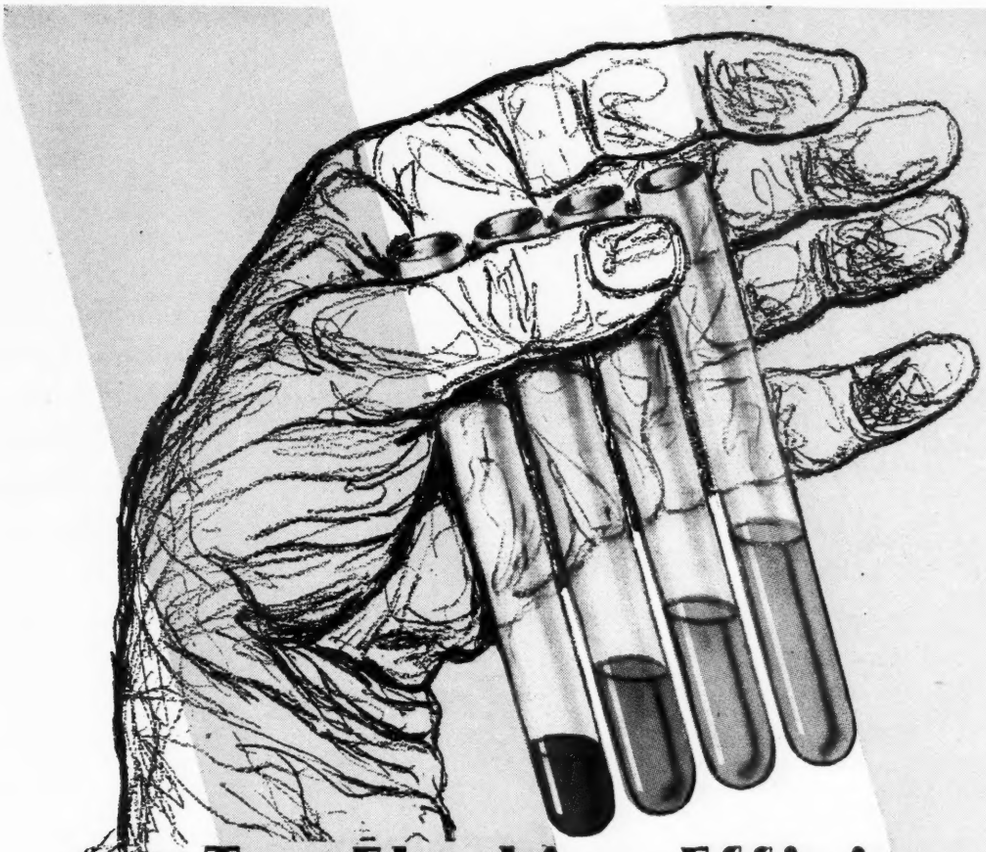

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Dehydrocholic acid	Hydrocholeretic	Stimulates secretion of fluid bile by the liver	+++	Utilizes copious amounts of free-flowing bile – adequate in absence of spasm of sphincter of Oddi
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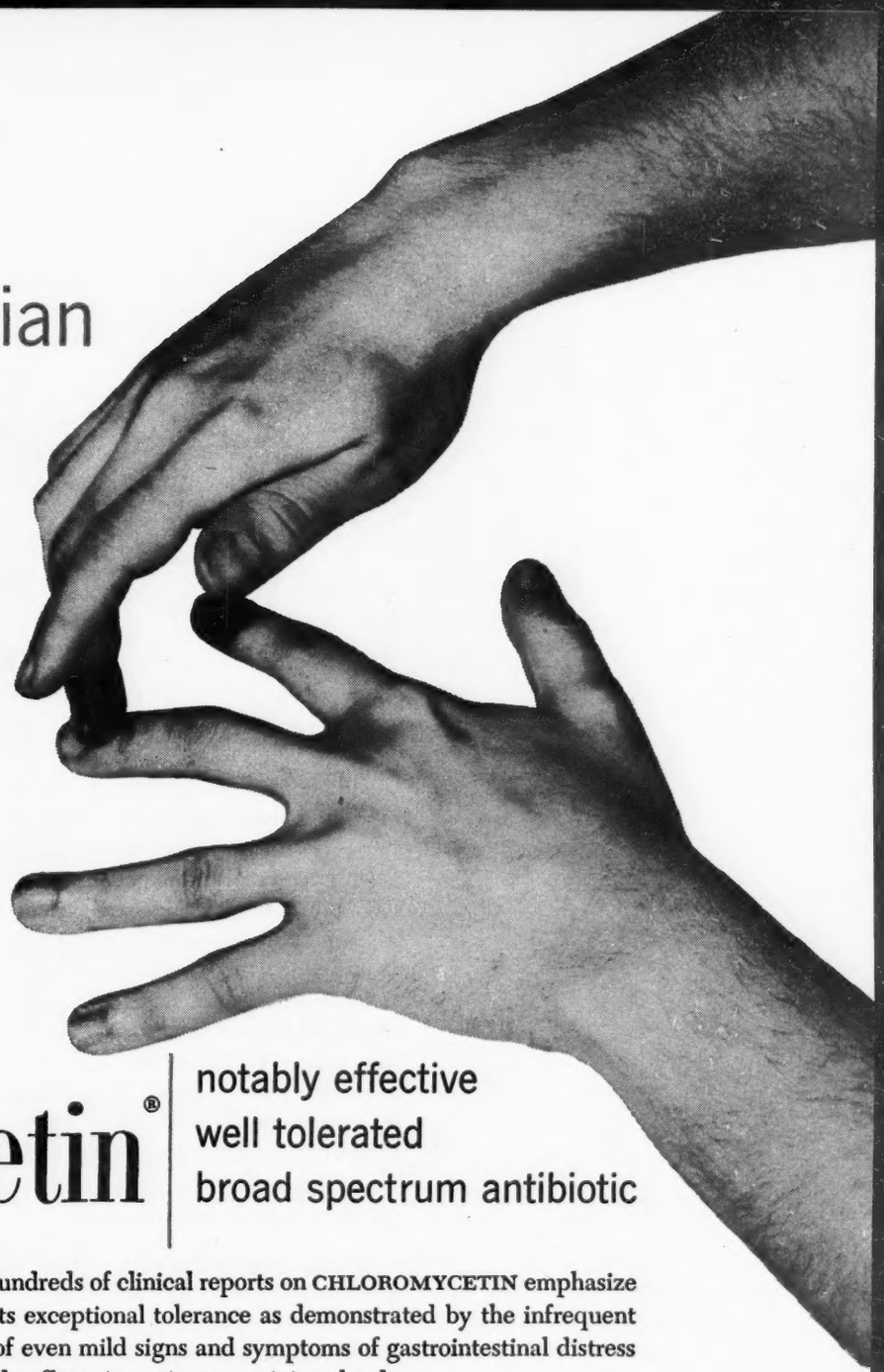

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*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.15 mg.	PANTOTHENIC ACID	3.0 mg.
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MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
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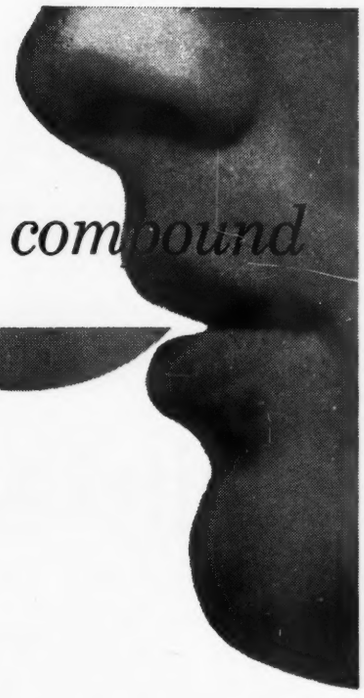
*Nutrients for which daily dietary allowances are recommended by the National Research Council.



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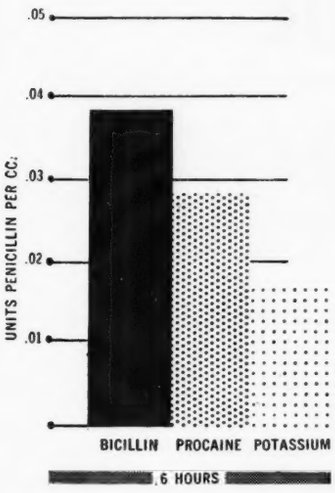

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1 teaspoonful (5 cc.), supplies 300,000 units (approximately 300 mg.).

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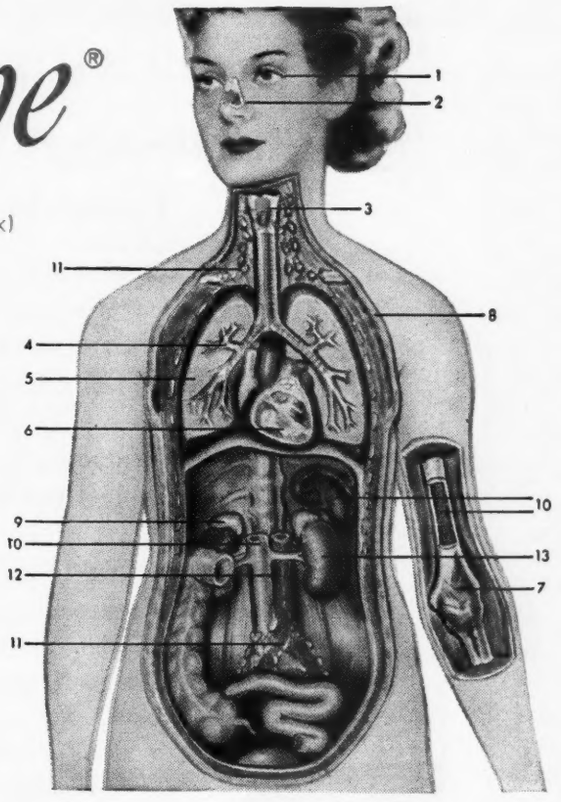

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1. EYE—Inflammatory eye disease. **2. NOSE**—Intractable hay fever. **3. LARYNX**—Laryngeal edema (allergic). **4. BRONCHI**—Intractable bronchial asthma. **5. LUNG**—Sarcoidosis. **6. HEART**—Acute rheumatic fever with carditis. **7. BONES AND JOINTS**—Rheumatoid arthritis; Rheumatoid spondylitis; Acute gouty arthritis; Still's Disease; Psoriatic arthritis. **8. SKIN AND CONNECTIVE TISSUE**—Pemphigus; Exfoliative dermatitis; Atopic dermatitis; Disseminated lupus erythematosus; Scleroderma (early); Dermatomyositis; Poison Ivy. **9. ADRENAL GLAND**—Congenital adrenal hyperplasia; Addison's Disease; Adrenalectomy for hypertension, Cushing's Syndrome, and neoplastic diseases. **10. BLOOD, BONE MARROW, AND SPLEEN**—Allergic purpura; Acute leukemia† (lymphocytic or granulocytic); Chronic lymphatic leukemia.† **11. LYMPH NODES**—Lymphosarcoma†; Hodgkin's Disease†. **12. ARTERIES AND CONNECTIVE TISSUE**—Periarteritis nodosa (early). **13. KIDNEY**—Nephrotic Syndrome, without uremia (to induce withdrawal diuresis). **14. VARIOUS TISSUES**—Sarcoidosis; Angioneurotic edema; Drug sensitization; Serum sickness; Waterhouse-Friderichsen Syndrome.

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The American Journal of Medicine

Vol. XIV FEBRUARY, 1953 No. 2

Editorial

The Eosinophil, ACTH, Epinephrin and Stress

EOSINOPHILS. The disappearance of eosinophils from the circulating blood has been known for many years to accompany certain serious pathologic conditions in man. The mechanisms which mediated this change were unknown but its clinical implication appeared well documented. The level of circulating eosinophils at any given moment must represent the balance which exists between production and liberation of these cells on the one hand and the rate of their destruction or disappearance from the blood stream on the other. With a hypoplastic bone marrow one might anticipate reduced cellular production whereas the presence of certain antigenic substances might stimulate a normal bone marrow to marked proliferation. Although substances which facilitate the disappearance of eosinophils from the circulating blood stream are now well established, the factors which favor the survival of these cells have not been clearly delineated.

Adrenal Steroids and ACTH. Of the substances capable of inducing eosinopenia, the adrenal cortical steroids are perhaps the best known. The "eosinopenic" potentiality is possessed most strikingly by those adrenal substances containing an oxygen atom in both the 11 and 17 carbon positions (cortisone and compound F). Eleven-oxygenated steroids such as corticosterone (compound B) and dehydrocorticosterone (compound A) are only mildly eosinopenic; 11-desoxycorticosterone and 11-desoxy-17-hydroxycorticosterone (compound S of Reichstein), dehydroisoandrosterone and adrenosterone possess little or no eosinopenic potentiality. In man the eosinopenia which follows adrenal cortical steroid administration can be demonstrated most easily by administering cortisone or hydrocortisone (compound F) orally or intravenously. Under these circumstances one notes a progressive decrease in circulating eosinophils which is proportional to the dose of steroid administration and the duration of the infusion, when the hormone is administered intravenously. Within the range of 30 to 90 per cent eosinopenia a dose-response curve can be established. Larger quantities of cortisone and 17-hydroxycortisone cannot be evaluated by this technic because of the almost complete disappearance of circulating eosinophils following moderate doses of hormone. The reliability of these observations in man is enhanced by carrying out the assays on patients with Addison's disease or in patients in whom a bilateral complete adrenalectomy has been performed.

From these observations it would be anticipated that were all other factors to remain constant, stimulation of the adrenal cortex by ACTH would be reflected by an eosinopenic response proportional to the total quantity of 11- and 11–17-oxysteroids released. The increased secretion of "non-eosinopenic" steroids would of course not be detected by this means. For practical purposes it has been possible to establish the integrity of the adrenal cortex by employing this simple screening procedure. An adequate number of circulating eosinophils must be present initially, however, for reliable interpretation. Recent studies indicate that the continuous intravenous infusion of ACTH is perhaps the most effective means of inducing maximal adrenocortical stimulation. Of course, the final evaluation of the adrenal cortical response following ACTH administration must include more direct measurement of adrenal activation such as the demonstration of an increased blood or urinary corticoid level or increased excretion of 17-ketosteroids.

Epinephrin. That the injection of epinephrin is also capable of inducing an eosinopenia has

been known for some time. With the marked interest evidenced recently in the possible contribution of the pituitary-adrenal axis to the stress response it was postulated that the eosinopenic effect observed with epinephrin could be explained by the enhanced secretion of endogenous ACTH and the consequent increased secretion of adrenal steroids. Experiments in man, however, indicated that epinephrin was also capable of inducing eosinopenia in patients following bilateral complete adrenalectomy. As methods for determining 11–17-oxysteroids became more generally available, studies were carried out in man in which changes in steroid blood level or urinary excretion were measured in conjunction with the changes in circulating eosinophils following epinephrin administration. In several laboratories it has been reported that the injection of epinephrin subcutaneously or intravenously in a variety of dose levels has *not* resulted in a significant increase in oxysteroid blood or urine levels or in an increased excretion of 17-ketosteroids despite the fact that the expected eosinopenic response occurred. Although such possibilities as "increased utilization" of adrenal hormone and altered renal excretion of corticosteroids have been proposed as possible explanations of the phenomenon, the fact remains that to date not a single conclusive experiment has been brought forward to support the hypothesis that epinephrin specifically stimulates endogenous ACTH formation in man! For the time being then, "epinephrin eosinopenia" in man must perforce be considered a phenomenon independent of adrenal cortical activation.

Stress. If one now turns his attention to experiments in man characterized by the exposure of the normal subject or patient to a known or "standardized" stress, an interesting situation exists. In almost every instance in which a stress of any magnitude is imposed, a significant eosinopenia develops. Is the eosinopenia a reflection of increased ACTH and adrenal cortical steroid secretion, or does it reflect predominantly the contribution of epinephrin or other less well known eosinopenic factors? By careful titration with ACTH in normal subjects it is possible to quantitate within the 30 to 90 per cent eosinopenic response the magnitude of the associated increase in excretion of urinary total "17-hydroxycorticoids." Having established this dose-response curve, one is then in the position of being able to approximate the degree to which a given eosinopenic response to stress is mediated by the adrenal cortex, and what proportion of the fall in circulating eosinophils must in all probability be explained by the release or secretion of other agents such as epinephrin. For example, the development of a marked eosinopenia, i.e., 90 per cent fall, in the presence of only a slight rise in urinary total "17-hydroxycorticoids" suggests that factors other than the adrenal cortical steroids of the 17-oxygenated type have participated in the production of the eosinopenia. Such a method of approach may prove helpful in analyzing the response of man to stresses of widely different types.

The response of the circulating eosinophil to ACTH, 11–17-oxysteroids and epinephrin is well established. Following ACTH administration one may reliably interpret the resulting eosinopenia in terms of increased secretion of 11–17-oxysteroids. There is no evidence to date to indicate that the eosinopenia induced by epinephrin in *man* is mediated by increased release of ACTH and adrenal corticosteroids. Thus the interpretation of the eosinopenia of stress must not be limited to a consideration of adrenal cortical activation alone but must include the concept of other participating eosinopenic agents of which epinephrin is a prototype. A suggestion has been made whereby an approximation of the participation of the adrenal cortex in the eosinopenic response to stress may be estimated.

GEORGE W. THORN, M.D.

Clinical Studies

Treatment of Essential Hypertension with β-Alkylamines, Especially Dibenzyline*

JOHN L. BAKKE, M.D. *and* ROBERT H. WILLIAMS, M.D.
Seattle, Washington

BECAUSE of a lack of understanding of the various factors in the pathogenesis of essential hypertension many therapeutic approaches have been investigated. During the past five years we have had the opportunity to study the effects of six adrenergic blocking agents of the β-alkylamine group after oral and/or intravenous administration to 103 patients with essential hypertension.

In order to clarify the background of such a study the following orientation is presented. Five factors are known to influence the blood pressure: (1) blood volume (2) viscosity (3) cardiac output (4) arterial elasticity and (5) peripheral resistance. In uncomplicated essential hypertension only the fifth factor, which is under humoral and neurogenic control, has been shown to be abnormal.

Hypertension has been brought about by producing lesions in selective areas of the nervous system as, for example, by denervating the carotid sinus and sectioning the aortic depressor nerve. However, experimental neurogenic hypertension does not mimic human essential hypertension as closely as does the hypertension produced by compression of the renal arteries or that produced by injection of the following substances: angiotonin, pherentasin, vasoexcitatory material (VEM) and desoxycorticosterone (DCA).[1] Nevertheless the nervous system, via the sympathetics, influences peripheral vascular resistance; consequently means of altering this effect have been investigated surgically and chemotherapeutically. The results of lumbodorsal sympathectomy in the treatment of essential hypertension have been satisfactory in only a minority of patients: Grimson[2] reports good results with a sustained fall in diastolic pressure of 20 mm. in 66 per cent of 113 patients, Evans and Bartels[3] in 47 per cent of 173 patients, Smithwick[4,5] in 37 per cent of 439 patients, White[6] in 22 per cent of 50 patients, Evelyn[7] in 21 per cent of 100 patients and Hoobler[8] in 29 per cent of 338 patients. Good responses do not imply that these patients had excessive neurogenic vascular tone but indicate that the removal of normal neurogenic support withdraws one element contributing to the maintenance of hypertension.

The variability of results following sympathectomy, as well as other evidence, indicates that the factors influencing the blood pressure vary in kind and/or degree in different patients; consequently the response to therapy may be expected to vary. No single approach may ever be found to benefit all or even a majority of patients. However, the high morbidity and mortality of essential hypertension warrant extensive exploration of any compound or procedure that will produce a lowering of blood pressure in even a small proportion of patients. Of course lowering the blood pressure does not correct the underlying causal mechanism nor does it reverse all disturbances that are associated with hypertension but unquestionably it will contribute to a reduction in myocardial enlargement and failure, renal damage, retinal damage and cerebrovascular accidents.[5]

Drugs intended to lower the blood pressure of patients with essential hypertension may be called "hypotensogenic agents." Such an agent should meet the following requirements: (1) lower the blood pressure significantly; (2) not unduly distress the patient or have significant toxicity; (3) relieve the symptoms and signs associated with hypertension; (4) require no more than three doses each day; and (5) be effective orally. Also, it is desirable but not

* From the Department of Medicine, University of Washington, the King County Hospital, and the Veterans Administration Hospital, Seattle, Wash.

essential that it benefit a large percentage of patients. Clinicians test scores of hypertensive patients for pheochromocytoma or coarctation of the aorta in order to benefit this group which comprises less than 1 per cent of the hypertensive population. It would appear to be equally reasonable to treat patients with essential hypertension with an agent effective in a similar small percentage.

Hypotensogenic agents may be classified according to their site of action as follows: (1) central vasomotor depressor agents such as the veratrum and ergot alkaloids; (2) autonomic ganglion blocking agents such as the quaternary ammonium compounds; and (3) peripherally effective adrenergic blocking agents such as the β-alkylamines.[9,10] This classification is tentative since future reports are likely to show that each of these compounds may act at several sites.

Among the newer *central vasomotor depressor agents* are the stable, biologically standardized extracts of Veratrum viride available in various oral preparations. The site of action of these compounds is still under study but there is evidence that they lower the blood pressure by depressing the vasomotor centers in the hind-brain causing peripheral vasodilatation, decreased peripheral resistance and increased vagal tone with bradycardia. They do not lower the blood pressure by direct myocardial effects nor do they block adrenergic impulses although, curiously enough, they are the only agents known to block the increased heart rate (positive chronatropism) resulting from epinephrine. Their clinical use has been severely curtailed by emetic properties and by a variable and limited effectiveness in lowering the blood pressure.[11–13]

Other central vasomotor depressor agents include the hydrogenated ergot alkaloids, which are also adrenergic blocking agents in high dosage; however, Goodman[14] points out that these drugs rarely if ever produce adrenergic blockade in man in tolerated doses; he states that the drop in blood pressure and reduction in heart rate are the result of central inhibition of the vasomotor center. Oral dihydroergocornine has been reported ineffective in lowering the blood pressure in preliminary clinical studies.[15] However, Kappert[16] claims both adrenergic blockade and clinical efficacy when the compounds are administered by the parenteral route.

The *autonomic ganglion blocking agents* include the quaternary ammonium compounds (tetraethylammonium chloride (TEAC) and tetraethylammonium bromide (TEAB)) and polymethylene-bistrimethylammonium compounds (pentamethonium (C-5) and hexamethonium (C-6) iodide and bromide (bistrium, Squibb). Unfortunately, these agents do not block the action of nor-epinephrine and they do block parasympathetic impulses as well as sympathetic, thus producing troublesome gastrointestinal atony and urinary retention. They may potentiate pressor responses to epinephrine and nor-epinephrine with serious clinical consequences.[17,18] Death from acute hypotension has also been reported.[19] These compounds have been found to have only a brief duration of action, are of variable effectiveness orally and have no established value in the long term management of hypertension[20–22] although parenterally they are claimed to be the most effective hypotensogenic agents now available.[23]

Adrenergic blocking agents are often called "sympatholytic" and "adrenolytic" compounds—an inappropriate designation since they neither cause lysis nor destruction of sympathetic fibers, epinephrine or nor-epinephrine, nor do they paralyze the contractile mechanism of smooth muscle cells. Thus they are presumed to act by metabolic competition or displacement of sympathin E at its site of action in the end organ,[9,10] i.e., they are adrenergic blocking agents. These agents may be divided into the following four groups: (1) benzodioxanes, including piperoxan (933 F, benodaine, Merck); (2) imidazolines, including benzazoline (priscoline, Ciba); (3) dihydroergotamines, including dihydroergocornine (DHO 180), dihydroergocristine (DCS 90), dihydroergokryptine (DHK 135) and the combination thereof, hydergine (CCK 179, Sandoz); (4) β-alkylamines, including dibenamine® (Smith, Kline & French) and 688 A or dibenzyline (Smith, Kline & French).

These compounds may produce a fall in blood pressure, particularly in the erect position, but the duration and degree of fall are quite variable in different patients and are not related directly to either the dosage or the completeness of adrenergic blockade.

The benzodioxanes are much more effective in blocking circulating nor-epinephrine than in blocking sympathetic nervous reflexes, the latter effect being obtained only with large doses. These compounds require parenteral injection for reproducible effectiveness and their action is rapid in onset and of short duration. Because of these properties piperoxan has become useful in

the diagnosis of pheochromocytoma since its injection almost uniformly causes an initial prompt decrease in hypertension if it is due to circulating nor-epinephrine. However, tachyphylaxis prevents prolonged use for therapeutic purposes.[24] Untoward pressor responses also may result from piperoxan, which appears to have sympathomimetic potentialities in susceptible patients[25] and has been reported to cause hypertensive encephalopathy.[26] Conversely, a false-positive fall in blood pressure may occur without a pheochromocytoma.[27]

The imidazolines have only a slight action in blocking sympathetic pressor reflexes and have many limiting side effects, including a direct action on smooth muscle, antihistaminic action and cardiac stimulation which may elevate the blood pressure.

The adrenergic blocking properties of the dihydroergotamine group are a matter of controversy, as already mentioned.

The β-alkylamines, including dibenamine (N, N-dibenzyl-b-chlorethylamine hydrochloride) and dibenzyline (688 A or N-phenoxyisopropyl-N-benzyl-β-chlorethylamine hydrochloride), produce blockade of the vasoconstrictor effects not only of circulating nor-epinephrine and epinephrine ("epinephrine reversal") but also of all adrenergic sympathetic reflexes. They differ from the benzodioxanes in their apparent ability to penetrate cells and block or displace epinephrine and nor-epinephrine (sympathin E?) at their site of action at the termination of sympathetic fibers. Also, unlike the benzodioxanes, β-alkylamines have not been reported to have any sympathomimetic actions. Oral dibenamine has been demonstrated to be effective in lowering the blood pressure in rats with renal hypertension.[9] Thus these compounds are most promising from the pharmacologic point of view and offer the following advantages over sympathectomy: They (1) act on all vascular beds, (2) avoid sensitization to epinephrine or nor-epinephrine, (3) leave intact those vasodilator fibers that run with sympathetic pathways, (4) are not irreversible and (5) avoid the risk, pain and expense of a surgical procedure.

The first member of the β-alkylamine family to receive clinical trial was dibenamine. In 1946 Hecht and Anderson[28] reported that a single intravenous dose of 4 to 6 mg./kg. produced a fall in blood pressure, especially when standing, usually maximal within six hours and noticeable for one to two days or longer. They also demonstrated that it prevented dark adaptation, blocked any reflex rise in blood pressure and produced "epinephrine reversal." Direct cardiovascular effects of epinephrine including the rise in cardiac output, changes in ventricular electrocardiographic complexes and pallor of the skin were not inhibited.

In 1948 Haimovici and Medinets[29] reported that intravenous dibenamine hydrochloride reduced the blood pressure of patients with benign essential hypertension but not malignant hypertension, with orthostatic hypotension lasting twenty-four to seventy-two hours after the infusion of 5 mg./kg. Wunsch et al.[30] reported that the intravenous infusion of 2 to 10 mg./kg. produced transient depression of supine blood pressure in each of fourteen patients with fixed hypertension, including ten in the malignant phase. Miosis, diuresis, increased urea clearance and temporary symptomatic remission of hypertensive encephalopathy were observed. All patients developed toxic reactions, including restlessness and mental confusion in nine patients, nausea and vomiting in eight, drowsiness in five and convulsions in one. More recently Barnett[31] reported the effectiveness of intravenous dibenamine in blocking the effects of nor-epinephrine given intravenously in doses of 0.15 to 0.34, μg./kg./min. This blockade lasted twenty-four to forty-eight hours. Nasal congestion, nausea, vomiting, confusion, toxic psychosis and thrombophlebitis were reported.

Attempts to use dibenamine orally were disappointing. Wunsch et al.[30] administered oral dibenamine in enteric-coated tablets to seventeen patients, with a definite fall in supine blood pressure in three, relief of headache in two (without lowering the blood pressure) and blockade of the cold pressor test in the five tested. Nausea and vomiting occurred in every patient, precluding continued clinical use of the drug.

We have undertaken the clinical trial of less toxic congeners of dibenamine in the hope of finding a useful hypotensogenic agent. It is the purpose of this report to present a preliminary clinical evaluation of six such drugs.

METHODS

Medications. Six closely related β-alkylamines*[32–34] have been administered orally,

* SKF 194, 199, 443, 501 and 688-A (dibenzyline) were kindly supplied by Dr. E. J. Fellows of the Smith, Kline & French Laboratories, Philadelphia, Pa. SY 28 was kindly supplied by Dr. E. A. Sharp of Parke, Davis & Company, Detroit, Mich.

intravenously or by both routes in this study. The structural formulas of the six compounds are illustrated in Figure 1. The capacity of all these compounds, except SY 28, to depress the excitatory (vasoconstrictor) effects of adrenalin* has been measured by Dr. E. J. Fellows. The pressure in a carotid artery of anesthetized cats (pentobarbital sodium) was recorded with a mercury manometer. The intravenous dose of adrenalin sufficient to give a blood pressure rise of 50 to 70 mm. Hg was determined. An arbitrary dose of the experimental compound was then injected intravenously after the blood pressure had returned to the usual range for the subject. The test dose of adrenalin was again injected. If the test dose produced a fall instead of the usual rise in blood pressure, the dose of adrenalin was increased until 1.0 mg./kg. was attained. When the pressor action of all test doses of adrenalin was reversed, the "paralyzing dose" of the adrenergic blocking agent had been attained. No attempt was made to determine the same potency figures in humans.

Oral therapy for our hypertensive patients consisted of giving enteric-coated tablets varying from 37.5 to 100 mg. or gelatin capsules containing 20 mg. Placebos of identical appearance were also used. The medication was administered with meals and at bedtime in increasing doses until either the blood pressure fell to normal or undesirable effects forced cessation of therapy.

For intravenous therapy the compound was dissolved in propylene glycol and added to 200 to 500 cc. of 5 per cent dextrose and injected within twenty to sixty minutes. The patient was usually semi-recumbent with the head of the bed elevated 45 degrees to accentuate orthostatic hypotension. The pulse and blood pressure were taken every two to four minutes by a physician. The drug was continued until there was a striking fall in blood pressure or an unresponsiveness to intravenous adrenalin ("epinephrine reversal") or nor-epinephrine.

Selection of Patients. One hundred three male and female patients with sustained essential hypertension were selected for study. Most of the patients had been observed both in the Medical Outpatient Clinic and in the hospital over months or years prior to this study. They had received the usual work-up appropriate in a teaching and research medical service including urinalysis, blood urea nitrogen, intravenous pyelogram, electrocardiogram, chest x-ray and an evaluation for sympathectomy when indicated. Many patients had a benzodioxane test, sodium amytal sleep test, caudal block, spinal block, and certain selected patients had an epinephrine test before, during and after treatment. No patients with acute or subacute myocardial infarction were included. Although congestive failure was the reason for admission in the majority of instances, no patients in congestive failure were included until their failure had either cleared or stabilized.

The group of sixty-two patients who received oral dibenzyline constitute the major part of this report. There were forty-six males and sixteen females, forty-three hospitalized and thirty-nine outpatients in this group. Their average age was 48.9 years, with a range of twenty-six to seventy years.

Plan of the Experiments. A control period of one to four weeks was obtained to evaluate any spontaneous changes in blood pressure. It was appreciated that the blood pressure may continue to fall gradually over a three-month control period. This possibility was evaluated by a consideration of the slope of fall during the control period compared with the abruptness of fall during treatment and of the rise in blood pressure following cessation of treatment. Whenever possible, observations were made during repeated courses of therapy alternating with placebo of identical appearance substituted on the same dosage schedule. In the group of forty-two patients receiving oral dibenzyline in the hospital an average of eleven days control before therapy, thirteen days of therapy and seven days after therapy was obtained—a total of thirty-one days hospitalization. However, some of the patients were studied throughout two to three months of hospitalization. During the initial control period many patients were excluded from this study because their blood pressure became normal. The blood pressure of the hospitalized patients was taken daily, supine and standing, at 6 A.M. and 1 P.M. Outpatients were seen at intervals varying from three times a week to once a week. They were required to lie down for ten to fifteen minutes until the blood pressure was constant. The blood pressure also was taken after the patient had stood for one minute. All blood pressures were determined with a mercury manometer.

When a patient responded to dibenzyline, an

* Adrenalin (Parke, Davis & Company, Detroit, Mich.) containing 18 to 30 per cent nor-epinephrine prior to 1951.

attempt was made to repeat the response after he was discharged from the hospital. If the medication failed to lower the blood pressure, nor-epinephrine was injected intravenously to determine whether the pressor effects of nor-epinephrine had been blocked by the dibenzyline. The nor-epinephrine test was repeated when the patient was receiving a placebo since there is individual variation in responsiveness to nor-epinephrine, since some hypertensive patients have an increased sensitivity to nor-epinephrine[35] and since comparisons were believed to be more valid if each patient served as his own control.

SIX β-ALKYLAMINES

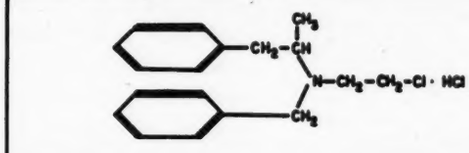
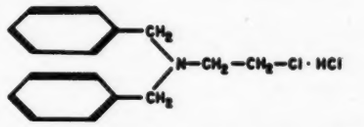
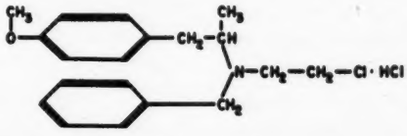
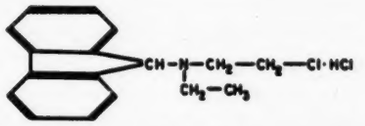
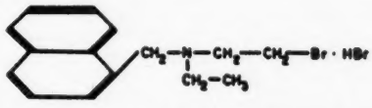
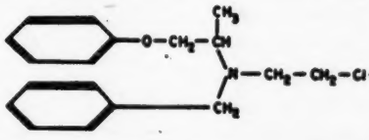
Compound	Structure	Epinephrine Paralyzing Dose (Cats)
SKF 194	 N-β-Chlorethyl-N-benzyl-β-phenyl-isopropylamine hydrochloride	5mgm/kgm
SKF 199 (Dibenamine)	 N-N-Dibenzyl-β-chlorethylamine hydrochloride	10mgm/kgm
SKF 443	 N-(p-Methoxyphenylisopropyl)-N-benzyl-β-chlorethylamine hydrochloride	5mgm/kgm
SKF 501	 N-(9-Fluorenyl)-N-ethyl-β-chlorethylamine hydrochloride	1mgm/kgm
SY-28	 (α-Naphylmethyl) ethyl-β-bromoethylamine hydrobromide	1mgm/kgm
SKF 688-A (Dibenzyline)	 N-(Phenoxyisopropyl)-N-benzyl-β-chlorethylamine hydrochloride	2.5mgm/kgm

FIG. 1.

Tabulation of Results. The tabulation of results in a study of this nature is relatively un-

satisfactory. One must decide whether to compare chiefly the changes in systolic pressures or diastolic pressures; moreover, changes with the patient in the supine and standing position must be evaluated. Whether to use the control period before treatment or one after treatment is a point of importance; the latter was selected when available. After the patient becomes ambulatory, another control period must be established. One may compare the mean of all values in a control period, placebo period, treatment period and post-treatment control period. This, however, will obscure a trend which may have appeared only toward the end of the therapeutic period when the highest dose of medication was being used. Also, since these agents appear to be effective for at least three or four days after cessation of medication, one must not include this period in the post-treatment control period, nor can one include it in the treatment period. The results in this study have been tabulated in several ways. Besides total means for each period the means of the three lowest values in the treatment period and in the control periods have been calculated. This is clearly open to criticism since data are being selected and the length of time in the two periods was not always comparable. However, it is preferable to the commonly reported method of selecting a single low point, which is more subject to technical error. A comparison of postural drop before and during treatment was also made. Lastly, a graphic presentation of the data was appraised for trends, which may be recorded as "impressions." This is probably the most useful of all methods but does not lend itself to objectivity or precision.

TABLE 1
SUMMARY OF INTRAVENOUS TESTS

Compound	SKF 194	SKF 443	SKF 501	Dibenzyline	Total
Number of patients	1	3	4	16	24
Number of experiments	1	11	11	17	40
Maximum single dose (mg.)	100	400	35	150	..
Hypotensive effect	0	+	+	+++	..

The patient's own evaluation of medication and placebo was noted, as well as any undesirable effects.

RESULTS

Intravenous Administration

Twenty-four patients were tested with one of the five β-alkylamines in forty experiments. (Table 1.) Sixteen patients received dibenzyline, the remaining eight one of the other compounds. Only two of the latter had a hypotensive response whereas eight patients had a marked fall after the infusion of dibenzyline. Some of these failures may have been due to inadequate dosage, as one patient had a good response on repetition the following day with a larger dose. Figure 2 illustrates typical responses to intravenous dibenzyline.

In one patient a fall in blood pressure occurred after only 3 mg. of dibenzyline had been infused. In general, those patients with the most prompt response required the smallest total dose. Conversely, some patients tolerated as much as 150 mg. without any fall in blood pressure, supine or standing.

Ten of the sixteen patients given dibenzyline intravenously later received dibenzyline orally. Whereas five of these ten patients had a dramatic fall in blood pressure after dibenzyline intravenously, only one patient (Fig. 3) showed a good response to dibenzyline orally as well as intravenously.

Untoward results were occasionally encountered. Shock developed in one patient whose hypertension was complicated by untreated myxedema. Adrenalin not only failed to raise this patient's blood pressure but also lowered it still further, as might be expected with "epinephrine reversal." However, the use of shock blocks to elevate the foot of the bed restored the blood pressure to levels adequate to relieve oliguria. The patient remained hypotensive in the supine position for twelve hours and had orthostatic hypotension for four days.

A sedative effect was prominent in the patients who received the larger doses of dibenzyline. These patients felt "relaxed," "sleepy," "tired," "dopey," "drunk"; in three instances sleep progressed to stupor and finally in two to coma. An analgesic effect was also noted. Several patients commented on the disappearance of headache and pre-existing incidental joint pain. The decreased sensitivity to noxious stimulation permitted the incision of a large furuncle without anesthesia in one patient. Conversely, two patients complained of a severe throbbing bilateral temporal headache one hour after the infusion stopped. SKF-443 caused marked excitement in one patient. Although SKF-443 caused vomiting in several patients, no gastrointestinal symptoms followed intravenous dibenzyline, which contrasts with its frequent occurrence after intravenous dibenamine.

Within thirty minutes of starting the infusion the majority of patients complained of a "flushed feeling," "dry mouth," "thirst," "stuffy nose" and "light-headedness" made worse on sitting up. A tachycardia when erect was noted in almost every case.

Twenty-three patients received courses of SKF 194, 199, 443, 501, and SY 28 without apparent effect on the blood pressure, so further studies with these agents were discontinued. All data and discussion that follow concern dibenzyline only.

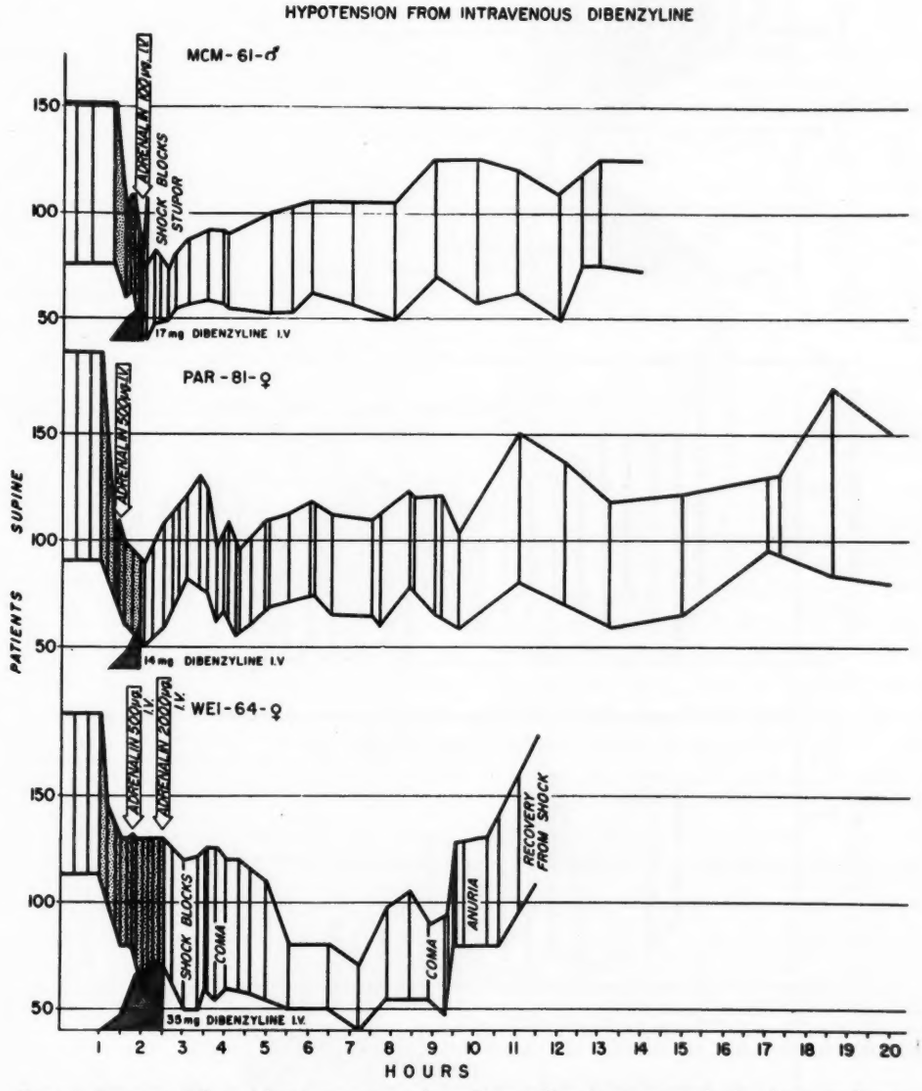


FIG. 2. Prompt fall in blood pressure after dibenzyline intravenously in three patients. The blood pressure remained below the control level for more than twenty-four hours. Adrenalin injections, designated by arrows, failed to elicit a normal pressor response and in two instances induced a fall in blood pressure ("epinephrine reversal").

The results of epinephrine and nor-epinephrine injection are detailed in the section dealing with adrenergic blockade.

Oral Administration

A total of eighty-five patients received one or several of the six drugs orally for a total of 1,086 patient-treatment days in courses varying from one day to one month. (Table II.)

Sixty-two patients received oral dibenzyline in eighty-two courses totalling 916 patient-treatment days. The maximum daily dosage varied from 37.5 to 2,500 mg. with a mean of 475 mg. The total dosage per course varied from 200 to 50,000 mg. with a mean of 3,470 mg.

Effect on Blood Pressure during Initial Course. During the initial course of therapy the mean of the three lowest standing control values

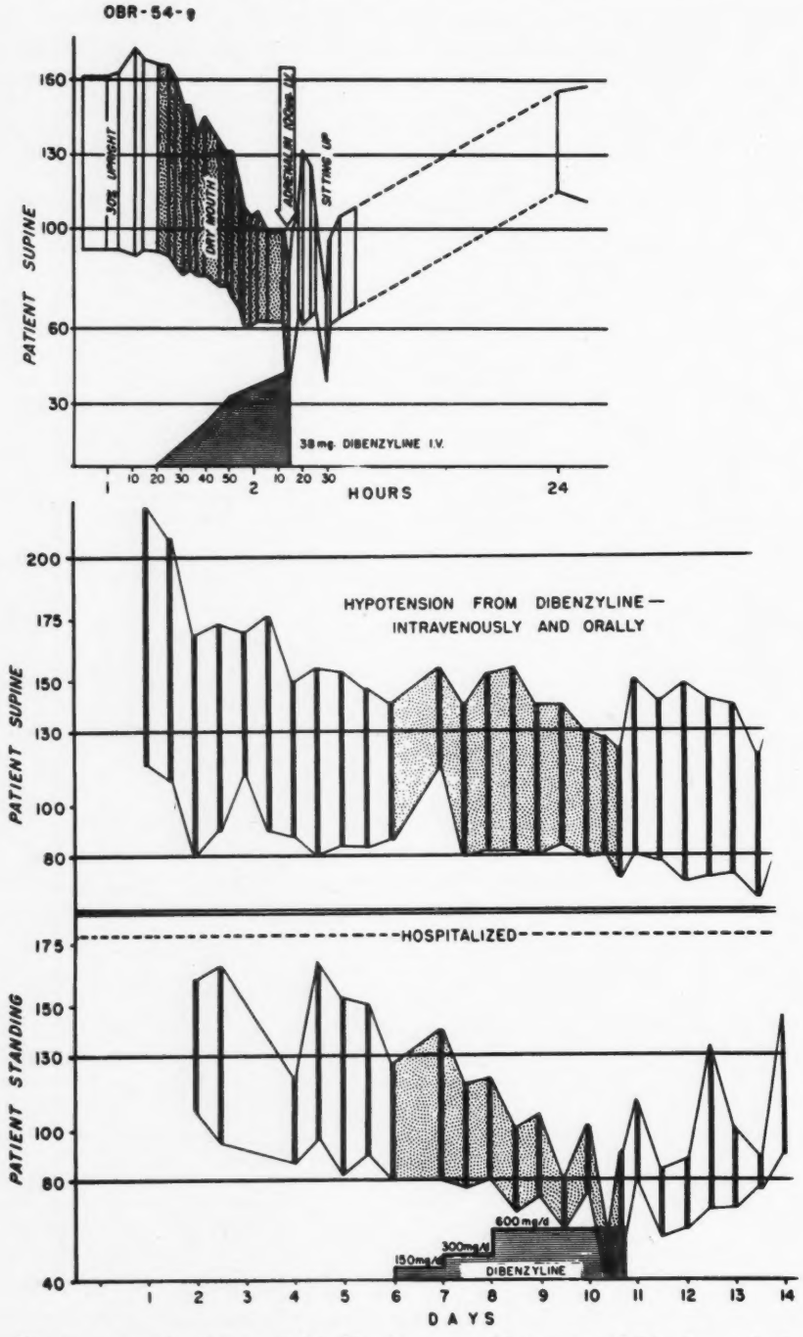


FIG. 3. As may be observed, this fifty-four year old woman exhibited a marked fall in blood pressure, supine and standing, upon the infusion of 38 mg. of dibenzyline given intravenously in fifty minutes. Adrenalin, 100 μg., injected intravenously caused a further fall in blood pressure associated with palpitation and blanching of the face and lips. After recovery, the patient was given dibenzyline orally for five days, starting with 150 mg., increasing to 600 mg. per day in divided doses. With the patient standing, a marked hypotensive effect was produced, lasting for three days after therapy was stopped. Thus this patient showed a good response to both intravenous and oral dibenzyline.

systolic and diastolic, contrasted with the three lowest standing treatment values, was tabulated and graded for each of the sixty-two patients.

The mean of all treatment and control values was also calculated. For reasons presented heretofore, these figures may obscure a definite response; however, they are free of any errors that might result from selecting data. Table III summarizes these data. As expected, the mean of the three lowest values gives a more favorable interpretation than a comparison of total means. Twenty-nine per cent had a good response in systolic pressure and 35 per cent had a good response in diastolic pressure by comparison of the means of three low points. If the total means are compared, only 18 per cent had a good response in systolic pressure and 13 per cent a good response in diastolic pressure.

The appearance of trends upon examination of the graphic presentation of the patient's data was thought to be a more accurate method of grading responses. Table IV presents some of the characteristics of the four groups of patients graded according to their response to an initial course of oral dibenzyline.

It will be noted that 33 per cent of the patients had a marked or definite response whereas 67 per cent had a doubtful or negative response. The sex and age distribution are the same in these two groups. A study of the clinical data of those patients who responded reveals no way by which their response might have been predicted. The majority of both groups had had hypertension at least five years, had had congestive failure and angina pectoris, an abnormal electrocardiograph, enlarged heart, decreased phenolsulfonphthalein excretion and grade II eye ground changes. Only three had an elevated creatinine and none who responded had grade IV eye ground changes or malignant hypertension.

The patients who failed to respond included not only those with malignant hypertension but also youthful patients with early labile hypertension that was associated with no renal or cardiovascular abnormality. It would appear that those who responded received slightly larger maximum doses of dibenzyline than those who failed to respond. However, the latter were at times given very large doses in an effort to produce a response.

For example, a thirty-seven year old white male was hospitalized with a blood pressure of 210/155. During a control period the mean pressure was 187/137 supine, 197/148 standing. During a placebo period the mean pressure was 192/139 supine, 203/147 standing. Despite 48,000 mg. of dibenzyline given over thirty-

TABLE II
SUMMARY OF ORAL ADMINISTRATION

Compound	SY 28	SKF 194	SKF 199	SKF 443	SKF #501	Diben-zyline	Total
Number of patients	8	3	3	4	5	62	85
Number of courses	9	3	3	12	12	89	128
Treatment days	86	11	52	15	6	916	1086
Hypotensive effect	0	0	0	0	0	+	....

TABLE III
INITIAL BLOOD PRESSURE RESPONSE TO ORAL DIBENZYLINE

Comparison of Mean of Three Low Points					
Grade of Response*	3+	2+	1+	0	Total
Systolic, No.	18	15	13	16	62
%	29	25	21	25	100
Diastolic, No.	21	5	7	29	62
%	35	8	11	46	100
Comparison of Mean of All Pressures					
Systolic, No.	11	13	11	27	62
%	18	21	18	43	100
Diastolic, No.	8	6	12	36	62
%	13	10	20	57	100

* A grade of "3+" (good) indicates a lowering of the systolic pressure by 40 or more mm. Hg, or the diastolic pressure by 25 or more mm. Hg; a grade of "2+" (fair) indicates a lowering of systolic pressure by 25 to 39 mm., or the diastolic pressure by 15 to 24 mm.; "1+" (poor) indicates a lowering of systolic pressure by 10 to 24 mm. or the diastolic pressure by 10 to 14 mm.; and "0" (failure) means a fall of less than 10 mm. in either systolic or diastolic pressure. This scale is taken from Gropper et al.[13]

TABLE IV
INITIAL BLOOD PRESSURE TRENDS OF RESPONSE TO ORAL DIBENZYLINE

Grade of Response	Marked	Defi-nite	Doubt-ful	Fail-ure	Total
Number of patients	8	12	17	25	62
Per cent of patients	13	20	28	39	100
Males, per cent of each group	75	80	71	70	72
Age, average (yr.)	51	52	49	46	49
Hospitalized, per cent of total	11	15	20	21	67
Outpatient Department, per cent	2	5	8	18	33
Average maximum daily dose (mg.)	589	489	363	527	475
Average days of therapy	14	13	7	10	11
Average total dose (mg.)	2,865	3,590	2,139	4,364	3,470

seven days, with a maximum daily dose of 2,500 mg. in addition to 24 mg. of veriloid each day, the mean pressure was 214/138 supine, 205/144 standing. Piperoxan and sodium amytal also failed to lower the pressure; but because the patient had a marked fall after a caudal block, a initial course of dibenzyline were given one or more additional courses. Fourteen of these patients failed to respond. Examples of this are shown in Figures 4 and 5.

Three of the six patients who responded to a second course of therapy were hospitalized.

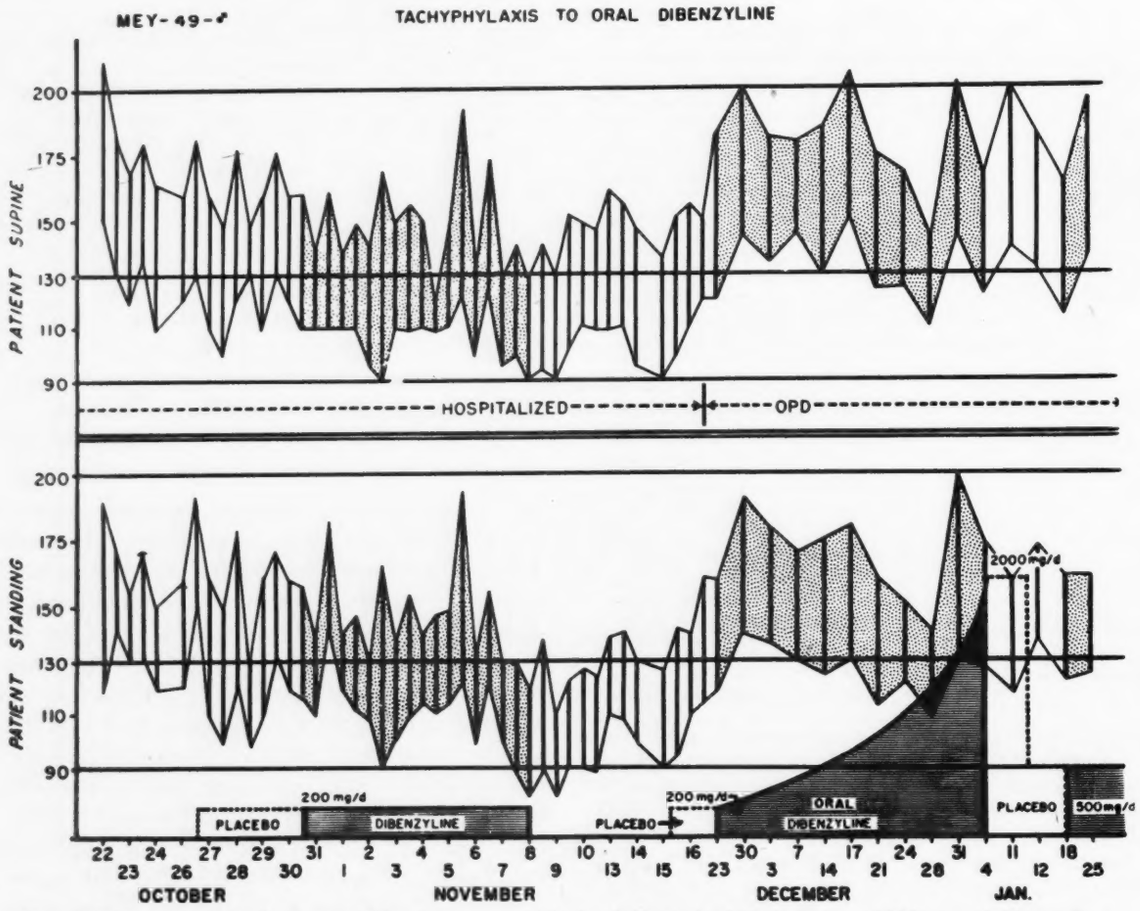


FIG. 4. Patient Mey. had a drop in blood pressure with the daily oral administration of 200 mg. of dibenzyline, but later the pressure remained elevated in spite of 2,000 mg. daily.

lumbodorsal sympathectomy was performed. The mean of 243 blood pressure determinations prior to surgery was 208/139. Between the first and the second stage of the sympathectomy the mean of twenty-nine blood pressure determinations was 203/141. After the second stage the blood pressure was unchanged. A course of dibenzyline, 20 mg. orally four times a day, for the first time produced a postural fall to 70/40 with a mean supine blood pressure of 167/113. When placebo was substituted, the blood pressure returned to its original level, a mean of 195/135.

Effect on Blood Pressure during Subsequent Courses. Twenty patients who had responded to an

These three had a good response during the first course of dibenzyline; and when placebo was substituted without their knowledge, a prompt rise in blood pressure occurred. Substituting dibenzyline for placebo again caused the blood pressure to fall. (Figs. 6 to 8.) However, even these three patients demonstrated neither convincing benefit from therapy nor continued responsiveness to prolonged administration of dibenzyline.

The remaining three patients who responded to a second course were outpatients. One showed a fall in blood pressure during a second course of ten days on 560 mg. per day but failed to show a significant fall during a third course.

The second patient had a good response to each of two courses of dibenzyline, 80 mg. daily, despite the fact that a pressor test with nor-epinephrine showed no blockade. This sensitivity to dibenzyline was thought to be due in part to a sympathectomy performed nine months before, although this procedure had failed to lower her pressure to normal. The response of the third patient is shown in Figure 9.

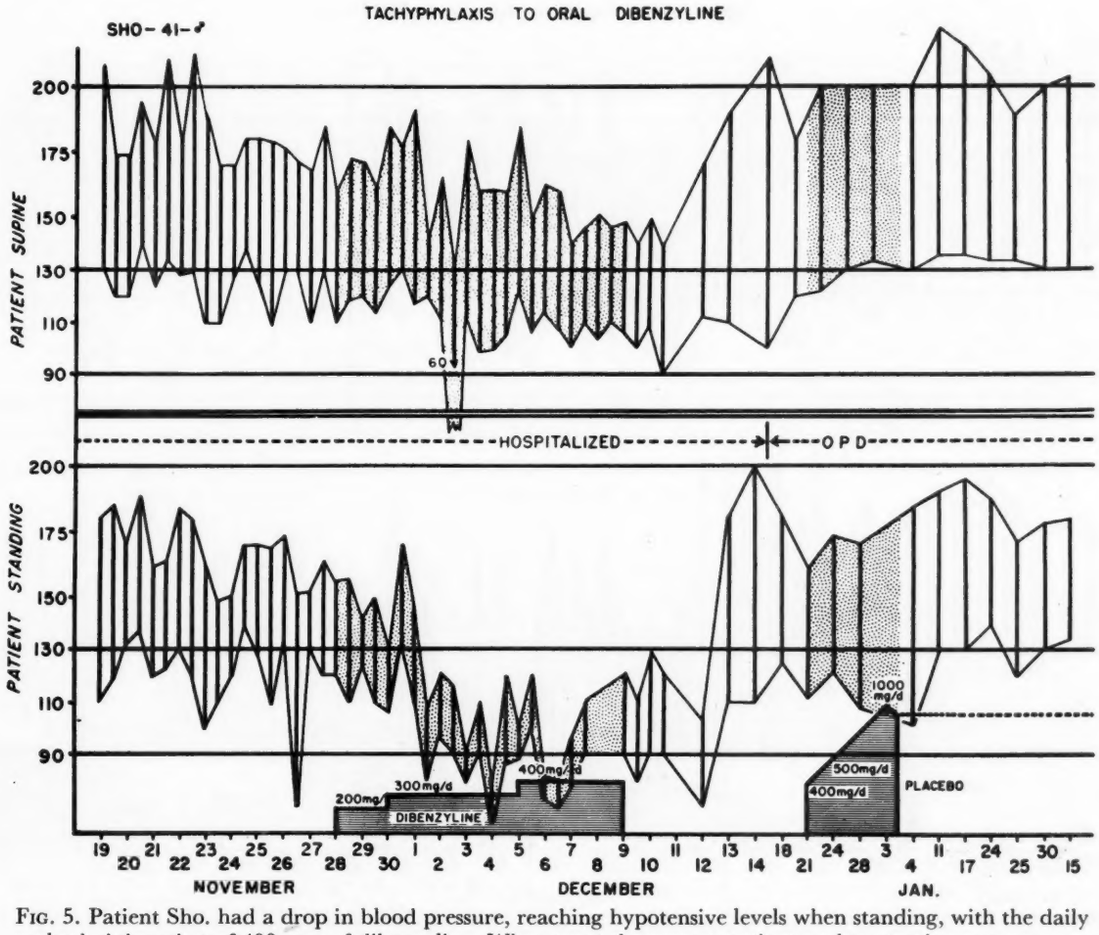


FIG. 5. Patient Sho. had a drop in blood pressure, reaching hypotensive levels when standing, with the daily oral administration of 400 mg. of dibenzyline. When treated as an outpatient no hypotensive response was obtained with the daily oral administration of 1,000 mg. A test with nor-epinephrine, conducted between the two courses of therapy, yielded a normal pressor response, and repetition of the test during the second course of dibenzyline showed (uncharted) complete adrenergic blockade to 600 μg. of nor-epinephrine, 0.2 μg./kg./min.

Duration of Action

Intravenous dibenamine is known to produce orthostatic hypotension which may be demonstrable for as long as five to six days after the supine pressure has returned to the control level.[17] As shown in Figure 2, the blood pressure remained down more than twenty-four hours. In several instances postural hypotension persisted three to four days. In the twenty-five patients who responded to oral dibenzyline and who were followed up in the hospital with frequent blood pressure determinations after cessation of therapy or substitution of placebo, it took a mean of 3.8 days (range one to seven days) for the blood pressure to return to the control level or for untoward effects to clear. However, adrenergic blockade was not demonstrated to last more than twenty-four hours.

Estimation of Adrenergic Blockade. Whenever orthostatic hypotension failed to result from dibenzyline, it seemed desirable to know whether or not adrenergic blockade had been accomplished. If blockade was not present, the possibilities that the patient was not taking the dibenzyline, that it had been inactivated, that it had not been absorbed from the gastroin-

testinal tract or that the daily dosage was too small were considered. Nor-epinephrine is preferable for this test but none was available in the early phase of our studies, so blockade was tested with adrenalin 1:1000, given intravenously or subcutaneously.

of "epinephrine reversal" of the blood pressure in some instances a waxy pallor of the face and a gasping and quickening of the respiration were common; multiple ventricular premature contractions were noted in two patients and auricular fibrillation made its appearance for ten

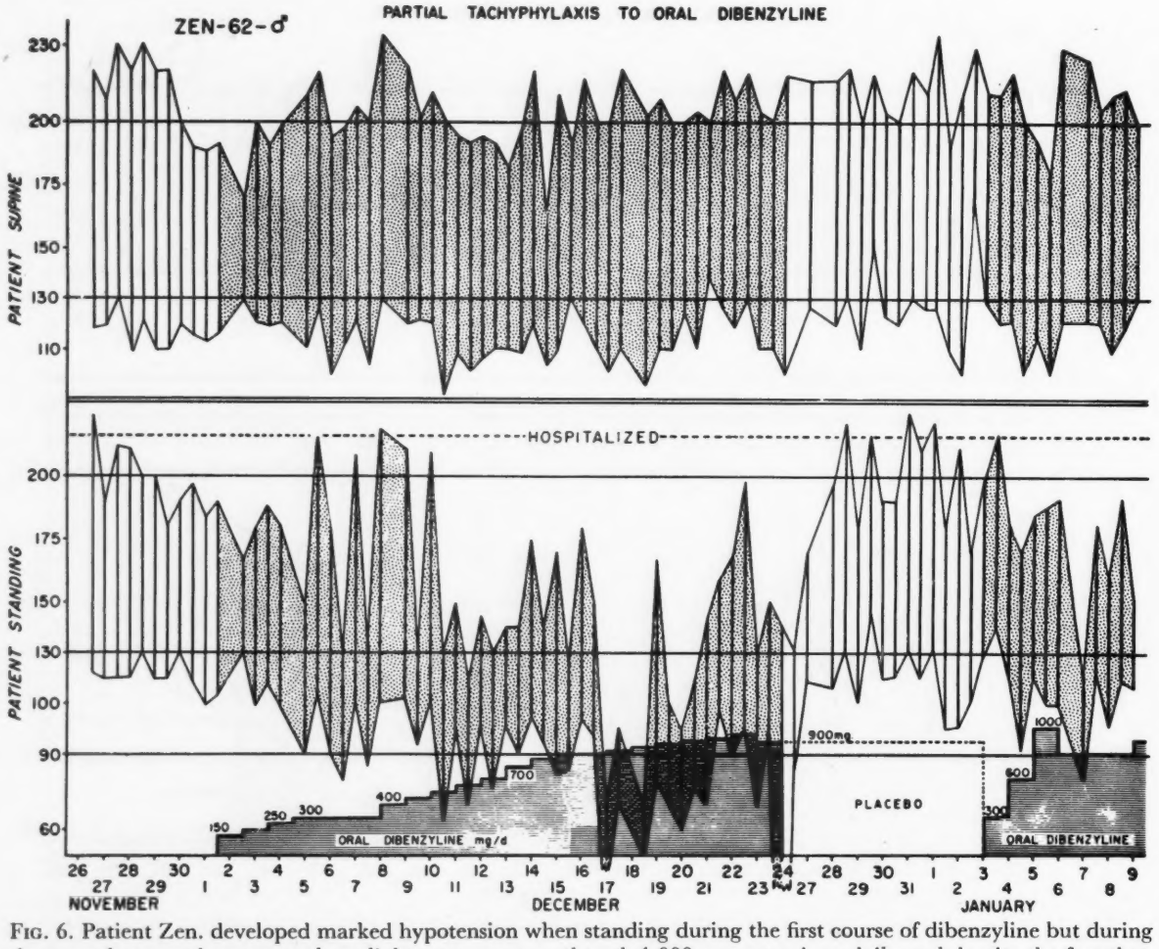


FIG. 6. Patient Zen. developed marked hypotension when standing during the first course of dibenzyline but during the second course there was only a slight response even though 1,000 mg. was given daily and despite the fact that it produced adrenergic blockade to 1,200 μg. of nor-epinephrine, 0.6 μg./kg./min., eleven hours after the last dose. During the control period 0.1μg./kg./min. produced a marked hypertensive response (uncharted).

In those patients receiving dibenzyline intravenously up to 0.5 cc. of adrenalin 1:1000 was injected intravenously over five seconds. All patients were observed to have a marked increase in the force of the precordial impact and alert patients complained of severe palpitation and anxiety. The pulse became bounding but usually did not show a marked change in rate. The blood pressure usually fell, the diastolic pressure falling more sharply than the systolic. In one patient there was a prompt rise in systolic blood pressure over 100 mm.; however, the diastolic pressure fell even in this instance indicating a fall in peripheral resistance. In spite

minutes in another. All patients receiving intravenous dibenzyline manifested some degree of epinephrine reversal when their response to adrenalin in the control period was compared. In addition, eight patients receiving oral dibenzyline were given adrenalin tests. Five of these tests indicated "epinephrine reversal" whereas the remainder were doubtful or negative. In four instances an absolute eosinophil count was performed before and four hours after the epinephrine with an eosinopenia of more than 50 per cent, indicating no blockage of epinephrine pituitary adrenal stimulation.

Nor-epinephrine tests were performed re-

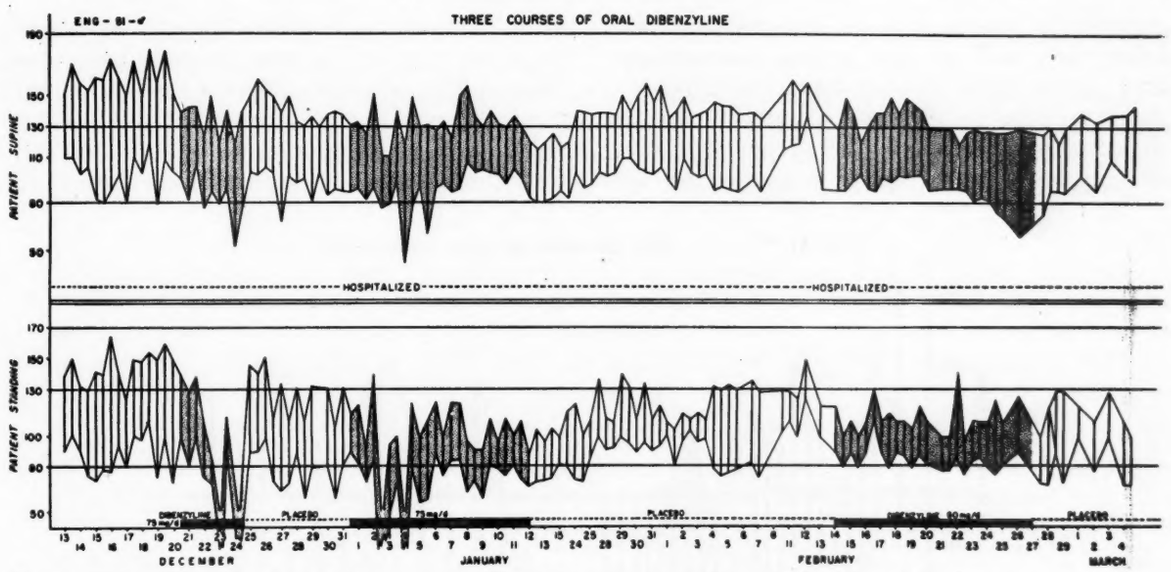


FIG. 7. Patient Eng. developed faintness on standing while receiving dibenzyline, 75 mg./day. When a placebo was substituted the blood pressure promptly returned to control levels. This was repeated three times during three months' hospitalization, during which time the control (placebo) blood pressure also became normal but without orthostatic hypotension. Partial blockade to nor-epinephrine, 0.5 μg./kg./min., was also demonstrated (not shown in chart).

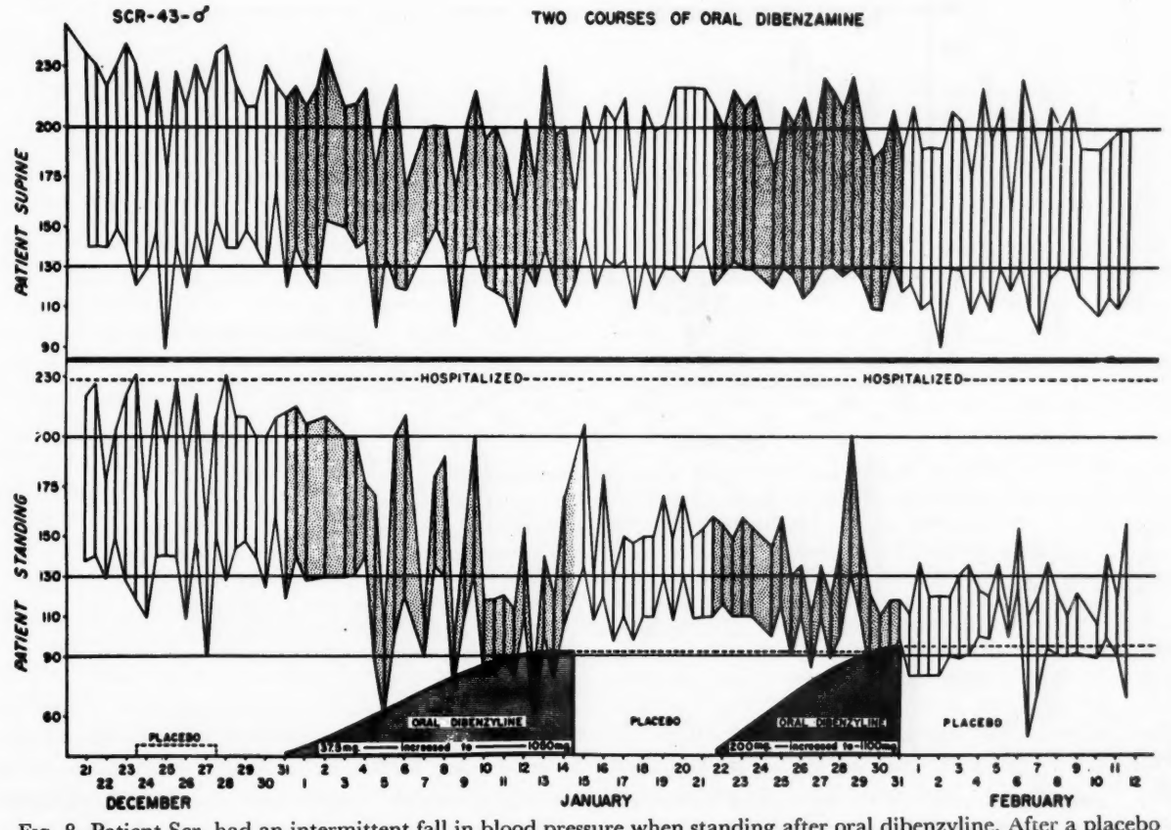


FIG. 8. Patient Scr. had an intermittent fall in blood pressure when standing after oral dibenzyline. After a placebo was substituted faintness, dizziness, indigestion and nasal congestion diminished over four days and the blood pressure rose but to a level less than the previous control period. A second period of therapy required 1,200 mg./day to produce orthostatic hypotension. The supine pressure did not fall and the third control period was again lower. A third period of therapy (uncharted) was of doubtful effectiveness because the baseline had become nearly normal. However, eleven hours after a 300 mg. dose of dibenzyline, blockade was present to 1,200 μg. of nor-epinephrine, 1 μg./kg./min. (uncharted).

peatedly in sixteen patients who received oral dibenzyline and in one patient immediately after intravenous dibenzyline. Initially the usually prescribed method of adding 4 mg. of nor-epinephrine* to 1 L. of 5 per cent dextrose was employed to deliver a recommended test dose of 10–14 μg./min. (0.1–0.2 μg./kg./min.).[36] However, because it soon became apparent that this solution was not concentrated enough to provide an adequate test of blockade, concencentrations as strong as 4 mg. in 100 cc. of 5 per cent dextrose were used. The calibrated drip rate was counted, as was the cumulative total dose during the test. During the placebo or control periods nor-epinephrine, 0.2 μg./kg./min., usually caused a rise in both systolic and diastolic pressures of more than 20 mm. Hg in addition to mildly unpleasant sensations in the chest and abdomen. During treatment with dibenzyline the same dose of nor-epinephrine failed to elevate the diastolic pressure. However, the toleration of larger doses was variable; some patients tolerated as much as 8.0 μg./kg./min. but most reacted to 1.0 μg./kg./min.

Even after 1,000 mg. of dibenzyline orally

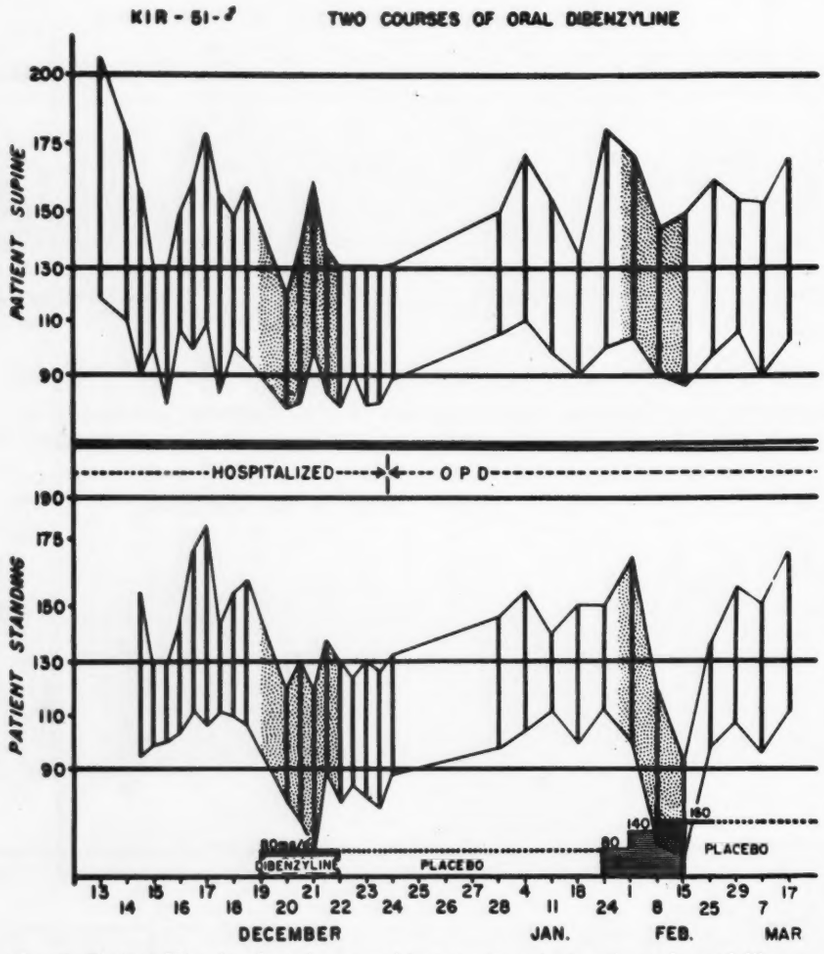


FIG. 9. Patient Kir. developed postural hypotension during three days of dibenzyline orally. Followed as an outpatient for one month the mean blood pressure was 160/100 supine, 149/107 standing. Dibenzyline, 140 mg./day, caused a prompt fall to 116/75 standing, with a return of nasal congestion and a malaise which prevented work. The blood pressure returned to control levels when again on a placebo. The pressor response to nor-epinephrine, 1.0 μg./kg./min., was only slightly less with this small dose of dibenzyline than during a placebo period (uncharted). Thus this patient developed standing hypotension on a dose insufficient to cause adrenergic blockade.

* Levophed, Winthrop-Stearns, which is stated by the manufacturers to contain less than 0.1 per cent epinephrine.

over twelve hours and 100 mg. intravenously over thirty-three minutes one patient manifested severe dyspnea, headache, pallor, anxiety, palpitations and a blood pressure rise from 170/120 to 240/145 within two minutes when given nor-epinephrine, 1.4 μg./kg./min. (Table v.) This patient failed to have any reduction in his grade IV hypertension after dibenzyline, caudal block, spinal block, piperoxan or prolonged hospitalization although the amytal sleep test reduced his pressure to 128/90.

TABLE V
NOR-EPINEPHRINE TESTS ON PATIENT HAL.

Conditions	Total Dose (μg.)	Total Time (min.)	Maximum Rate μg./kg./min.	Baseline B.P.	Maximum Response	Symptoms	Adrenergic Blockade
Control	40	2	0.26	190/142	240/170	Dizzy, warm legs	No
Control	40	4	0.13	178/135	235/160	Dizzy, warm legs	No
Dibenzyline 360 mg./day	190	10	0.24	170/130	190/120	0	Yes
Dibenzyline 360 mg./day	130	4	0.47	190/120	208/130	Palpitations	Yes
Dibenzyline 360 mg./day	160	5	0.50	202/122	195/120	0	Yes
Dibenzyline 1,000 mg. p.o. 100 mg. i.v.	200	2	1.4	170/120	250/145	Headache, palpitation, distress, pallor	No

Absolute eosinophil counts made before and after nor-epinephrine showed no fall in three instances. Samuels et al.[37] reported that nor-epinephrine does not elicit eosinopenia.

Effect on Symptoms. In spite of our observations that about one-third of the patients had a decrease in blood pressure during an initial course of oral dibenzyline only 13 per cent of the patients reported any subjective improvement. These patients were especially pleased with the relief of headache or angina pectoris, permitting discontinuation of nitroglycerine in two cases. Desirable sedative effects with increased relaxation and sounder sleep at night were noted. One patient claimed that dibenzyline cured his bronchial asthma. Another manifested prompt and complete relief of Raynaud's phenomenon. The patients who thought dibenzyline was helpful were also well aware that it had lowered their blood pressure and were anxious to cooperate.

Contrariwise, 87 per cent of the patients considered dibenzyline to be an unpleasant medication. They invariably had a strong preference for the placebo. This pessimistic evaluation suggests that psychologic influences were not important in lowering the blood pressure in these patients.

Undesirable Effects of Oral Dibenzyline. The most common complaint of patients receiving oral dibenzyline was nasal congestion, which was often mistaken for coryza and was noted by 87 per cent. The 8 per cent who had epistaxis, which they attributed to dibenzyline, may have been correct since it is reasonable to suppose that the unopposed parasympathetic vasodilatation of the nasal mucosa would predispose it to vascular accidents.

"Dizziness" without actual vertigo was the second most common complaint, occurring in 68 per cent. It was worthy of note that it need not be associated with orthostatic hypotension although this was frequently the case. Syncope was rare although many patients stated they were close to fainting before they achieved relief in a nearby chair or bed. This was especially noted upon rising in the morning and was severe in three patients who had sympathectomies and one with diabetic neuritis of the

sympathetic nerves and pre-existing orthostatic hypotension.

Indigestion, usually vague in description but occasionally an epigastric burning distress, occurred in 54 per cent. Anorexia and nausea were equally frequent and occasional vomiting was common when the dosage was increased to high levels. Aluminum hydroxide gel gave some relief.

A sensation of being tired, weak, "dopey" or "washed out" was the complaint of 31 per cent and so interfered with working that it was the stated reason for refusing further dibenzyline in several instances.

Patients also complained of trembling, difficulty in reading, blurred vision, a bad taste in the mouth, dry mouth, thirst, drooping eyelids, nightmares, palpitations and shortness of breath which they attributed to the medication.

Observation of the patients in the hospital confirmed many of these undesirable effects. The nasal congestion failed to respond to ephedrine intranasally. Tachycardia was also noted in many patients and on one occasion paroxysmal auricular tachycardia occurred. Carotid sinus hypersensitivity was observed. It was of interest that two patients refused inert placebo because it caused indigestion but later tolerated dibenzyline without this complaint.

These untoward symptoms all tended to decrease if the dibenzyline dosage schedule was continued unchanged. Thus by gradual increments large doses of dibenzyline were tolerated. This development of "resistance" was usually paralleled by a decrease in hypotensive effect.

COMMENTS

Since this study was performed two other reports have appeared. Haimovici et al.[38] administered oral dibenzyline to forty-seven subjects including twenty-eight ambulatory hypertensive patients, comparing mean control values with "the lowest supine blood pressure." These investigators reported that when the blood pressure was lowered the maximum effect occurred in one to one and a half hours after administration with gradually diminishing effects over three to five hours, an observation we were unable to confirm. They observed tachycardia, accentuated by standing, which we also noted.

Nine of their twenty-two hypertensive patients who had symptoms claimed symptomatic improvement, three times the percentage so benefited in our series. They also reported incomplete blockade of the cold pressor test, miosis which was resistant to neosynephrine, and improvement in electrocardiogram and fundi in two patients. They encountered only "few and minor" side reactions including dry mouth, stuffy nose, drowsiness, fatigue, weakness and rare nausea and vomiting. Orthostatic dizziness and palpitation were reported but "with proper adjustment of the dosage the patients displayed little of the above symptoms." Whereas we noted diminished effectiveness of the drug within a month, they report loss of response after two to three months—not until five to seven months in two individuals. Seven cases remained responsive over an eleven-month period. They also noted that ambulatory patients required higher doses than hospitalized patients; however, their experience in this regard was not as pessimistic as ours.

They do not report individual data but eight patients with essential hypertension showed a mean fall of 37/21 (supine) and 40/23 (erect). By the criteria we have used this would be a grade of "3+/2+" or a good response. They achieved these results with an average daily dose of 130 to 194 mg. (range 20 to 230 mg.), significantly lower than the dosage used in this study. Although without individual data comparisons cannot be made accurately, it is apparent that they consider dibenzyline to have more beneficial effects than we do.

More recently Allen and associates[24] have summarized their experience with intravenous dibenzyline in thirteen patients with essential hypertension and orally in fifteen patients. They report that doses varying from 0.7 to 1.0 mg./kg. given during 50 to 120 minutes produced a dramatic fall in blood pressure in the majority of instances, lasting two to nineteen hours after the injection was stopped. They also report nasal congestion, tachycardia, drowsiness, dry mouth, blurred vision, a complaint of fatigue and the sensation of being "drunk."

As in our experience, the oral administration of dibenzyline was "much less dramatic and the dosage is extremely variable"; details are not presented.

One patient with a malignant pheochromocytoma failed to maintain a response to intravenous benzodioxan, regitine, priscoline® or dibenamine but responded to dibenzyline. Twenty milligrams of dibenzyline given orally every two hours was "life saving"; "signs of

congestive heart failure disappeared rapidly, sensorium which had been clouded returned to normal, and appetite and strength improved rapidly."

It is not within the scope of this paper to attempt a comparison between β-alkylamines and the other hypotensogenic agents. However, it may safely be said that all fail to lower the blood pressure significantly in the majority of patients with essential hypertension; the salient fact is that they do lower it in a few patients. Is it the same minority for different agents? Detailed studies of four patients with courses of protoveratrine intravenously and orally, hexamethonium intravenously, veriloid, veriloid-phenobarbital-mannitol and dibenzyline orally have been made by Bruce and Paine,[39] using the standardized treadmill exercise tolerance test to derive a physical fitness index (PFI)[40] for each control and treatment period. The PFI was slightly improved in two patients during the administration of dibenzyline orally. In no instance did oral therapy produce a sustained significant fall in blood pressure; however on several occasions protoveratrine orally produced a decline in blood pressure and a marked improvement in the PFI for a few days.

Since different hypotensogenic agents act at different sites, it seems reasonable to combine them hoping their hypotensogenic but not their undesirable effects will be additive. The combination of veriloid, which acts centrally and causes bradycardia, with dibenzyline, which acts peripherally and causes tachycardia, would seem worthy of investigation. However, preliminary trial has not been promising. It has already been reported that Veratrum viride and dihydroergocornine used together lower the pressure in selected patients in whom neither one alone is effective.[41,42] Likewise, sympathectomy and salt-free diet together may be more effective than either procedure used alone.[43] This may explain why three patients in this series who had had sympathectomy (without a return to normal pressure) were especially sensitive to the effects of dibenzyline. Further trial in such sympathectomy failures would appear warranted.

SUMMARY AND CONCLUSION

1. Clinical studies with six congeners of dibenamine (N,N-dibenzyl-β-chlorethylamine hydrochloride) have been carried out during the past five years on 103 patients.

2. Forty intravenous infusions were given to twenty-four patients. One-half of the patients who received dibenzyline intravenously in doses of 7 to 150 mg. had a fall in blood pressure with associated adrenergic blockade and occasional untoward effects including shock, stupor and coma. Postural hypotension persisted for one to four days after the injection.

3. Eighty-five patients received 128 courses of oral therapy. Of the six compounds, only dibenzyline (688-A or N-phenoxyisopropyl-N-benzyl-β-chlorethylamine hydrochloride) was effective. Sixty-two patients received eighty-five courses of dibenzyline over 916 patient-therapy days. Doses ranged from 37.5 to 2,500 mg. per day, with a mean of 475 mg. per day.

4. Thirteen per cent showed a marked decrease in blood pressure and another 20 per cent a definite though less pronounced effect. Sixty-seven per cent failed to respond. Hospitalized patients responded more frequently and to a greater degree than outpatients. There was no way of predicting which patients would respond. Most of those who had shown a good response while in the hospital failed to respond to increased doses when outpatients. Only 13 per cent reported symptomatic benefit from dibenzyline. There was no correlation between those claiming subjective benefit and those showing objective benefit.

Eighty-seven per cent reported nasal congestion, 68 per cent dizziness, especially upon standing, 54 per cent indigestion, anorexia, nausea and occasional vomiting, 31 per cent fatigue and weakness, 8 per cent epistaxis and others reported blurred vision, palpitations and shortness of breath. Undesirable effects diminished with continued therapy but hypotensogenic effects also diminished.

Adrenergic blockade was evaluated by norepinephrine intravenously in forty-four tests and with adrenalin intravenously or subcutaneously in forty-five tests. There was no correlation between the presence or absence of adrenergic blockade and the patient's therapeutic response.

5. Dibenzyline administered orally appears to be of limited value in the treatment of essential hypertension; however, in a disorder with such a high morbidity and mortality any agent benefiting even a small minority of patients deserves careful study. Further clinical investigation of dibenzyline, especially in combination

with other hypotensogenic agents and procedures, would seem to be indicated.

Acknowledgment: We are very grateful to Dr. Walter F. Rogers, Jr. (now at the School of Medicine, Syracuse University) for his many contributions in the early phases of these studies.

REFERENCES

1. Corcoran, A. C., Page, I. H., Masson, G. M. C., Taylor, R. D. and Dustan, H. Hypertension and hypertensive cardiovascular disease. *Arch. Int. Med.*, 87: 732, 1951.
2. Grimson, K. S., Orgain, E. S., Anderson, B., Broome, R. A. and Longine, F. H. Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy, and celiac ganglionectomy. *Ann. Surg.*, 129: 850, 1949.
3. Evans, J. A. and Bartels, C. C. Results of high dorsolumbar sympathectomy for hypertension. *Ann. Int. Med.*, 30: 307, 1949.
4. Smithwick, R. H. Surgical treatment of hypertension. *Am. J. Med.*, 4: 744, 1948.
5. Smithwick, R. H. Hypertensive cardiovascular disease. *J. A. M. A.*, 147: 1611, 1951.
6. White, P. D., Dimond, E. G. and Williams, A. Follow-up study of one hundred private hypertensive patients with cardiovascular complications. *J. A. M. A.*, 143: 1311, 1950.
7. Evelyn, K. A., Alexander, F. and Cooper, S. R. Effect of sympathectomy on blood pressure in hypertension. *J. A. M. A.*, 140: 592, 1949.
8. Hoobler, S. W., Manning, J. T., Paine, W. G., McClellan, S. G., Helcher, P. O., Renfert, H., Peet, M. M. and Kahn, E. A. Effects of splanchnicectomy on the blood pressure in hypertension. *Circulation*, 4: 173, 1951.
9. Nickerson, M. and Goodman, L. S. Pharmacological properties of a new adrenergic blocking agent (dibenamine). *J. Pharmacol. & Exper. Therap.*, 89: 167, 1947.
10. Nickerson, M. and Nomaguchi, G. M. Locus of the adrenergic blocking action of dibenamine. *J. Pharmacol. & Exper. Therap.*, 93: 40, 1948.
11. Coe, W. S., Best, M. M. and Kinsman, J. M. Veratrum viride in the treatment of hypertensive vascular disease. *J. A. M. A.*, 143: 5, 1950.
12. Wilkins, R. W. Veratrum viride and essential hypertension. *New England J. Med.*, 242: 535, 1950.
13. Gropper, A., Surtshin, A. and Hedrick, J. Effects of veriloid on essential hypertension. *Arch. Int. Med.*, 87: 789, 1951.
14. Goodman, L. S. and Nickerson, M. Clinical applications of adrenergic blockade: a critical appraisal. *M. Clin. North America*, 34: 379, 1950.
15. Bello, C. T., Moss, W. G. and Weiss, E. Effect of orally administered dihydroergocornine (D.H.O. 180) on hypertension. *Am. J. Med.*, 8: 634, 1950.
16. Kappert, V. A. Untersuchungen über die Wirkungen neuer dihydrierter Mutterkornalkaloide bei peripheren Durchblutungsstörungen und Hypertonie. *Helvet. med. acta* (suppl. 22), 16: 1, 1949.
17. Page, I. H. and Taylor, R. D. Augmentation of vasoactive substances by tetraethylammonium chloride. *Circulation*, 1: 1233, 1950.
18. St. Clair, W. R. and Stone, C. A. Potentiating effect of tetraethylammonium on pressor response to epinephrine and nor-epinephrine. *Proc. Soc. Exper. Biol. & Med.*, 77: 542, 1951.
19. Lasser, R. P., Rosenthal, N. and Loewe, L. Death following use of tetraethylammonium chloride. *J. A. M. A.*, 139: 153, 1949.
20. Hoobler, S. W., Moe, G. K. and Lyons, R. H. The cardiovascular effects of tetraethylammonium in animals and man with special reference to hypertension. *M. Clin. North America*, 33: 1, 1949.
21. Mackey, W. A. and Shaw, G. B. Oral hexamethonium bromide in essential hypertension. *Brit. M. J.*, 2: 259, 1951.
22. Locket, S., Swann, P. G. and Grieve, W. S. M. Methonium compounds in the treatment of hypertension. *Brit. M. J.*, 1: 778, 1951.
23. Smirk, F. H. and Alstad, K. S. Treatment of arterial hypertension by penta- and hexamethonium salts. *Brit. M. J.*, 1: 1217, 1951.
24. Allen, E. V., Bannon, W. G., Upson, M., Huizenga, K., Bastron, J. and Waugh, J. A new sympatholytic and adrenolytic drug. Clinical studies on pheochromocytoma and essential hypertension. *Tr. A. Am. Physicians*, 64: 109, 1951.
25. Bierman, H. R. and Partridge, J. W. Untoward reactions to tests for epinephrine-secreting tumors (pheochromocytoma). *New England J. Med.*, 244: 582, 1951.
26. Green, D. M. qnd Peterson, E. M. Hypertensive encephalopathy after administration of benzodioxan. *J. A. M. A.*, 142: 408, 1950.
27. Soffer, A. False positive reaction to the piperoxan hydrochloride test for pheochromocytoma. *J. A. M. A.*, 148: 538, 1952.
28. Hecht, H. H. and Anderson, R. B. The influence of dibenamine (N, N-Dibenzyl-β-Chloroethyl-Amine) on certain functions of the sympathetic nervous system in man. *Am. J. Med.*, 3: 3, 1947.
29. Haimovici, H. and Medinets, H. E. Effect of dibenamine on blood pressure in normotensive and hypertensive subjects. *Proc. Soc. Exper. Biol. & Med.*, 67: 163, 1948.
30. Wunsch, R., Warnke, R. and Myers, G. The effect of dibenamine on severe hypertension. *Ann. Int. Med.*, 33: 613, 1950.
31. Barnett, A. J. Observations upon the effects of "dibenamine" in man, with special reference to its adrenolytic and noradrenolytic action. *M. J. Australia*, 1: 939, 1951.
32. Kerwin, J., Hall, G., Nickerson, M., Gump, W., McLean, R., Fellows, E. and Ullyot, G. The reported adrenergic blocking action of β-haloethylammonium compounds. *Science*, 113: 315, 1951.
33. Nickerson, M. and Nomarguchi, G. Adrenergic blocking action of phenoxyethyl analogues of dibenamine. *J. Pharmacol. & Exper. Therap.*, 101: 379, 1951.
34. Kerwin, J. F., Hall, G. C., Milnes, F. J., Witt, I. H., McLean, R. A., Macko, E., Fellows, E. J. and Ullyot, G. E. Adrenergic blocking

agents. III. N-(Aryloxyisopropyl)-beta-haloethylamines. *J. Am. Chem. Soc.*, 73: 4162, 1951.

35. GOLDENBERG, M., PINES, K. L., BALDWIN, E. DE F., GREENE, D. G. and ROH, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. *Am. J. Med.*, 5: 792, 1948.
36. SUTTON, G. C., KAPPERT, A., REALE, A., SKOGLUND, C. and NYLIN, G. Studies on L-nor-epinephrine: relation of dosage to pressor and bradycardia effect. *J. Lab. & Clin. Med.*, 36: 460, 1950.
37. SAMUELS, A. J., HECHT, H. H., TYLER, F. and CARLISLE, R. Leukocyte changes following intramuscular injection of epinephrine and epinephrine congeners, with observations on the alterations induced by adrenergic blocking agents. (Abstract.) *Am. J. Med.*, 8: 533, 1950.
38. HAIMOVICI, H., MOSER, M. and KRAKAUER, H. Effect of oral 688A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine Hydrochloride) on blood pressure in normotensive and hypertensive subjects. *Proc. Soc. Exper. Biol. & Med.*, 77: 477, 1951.
39. BRUCE, R. A and PAINE, R. M. Unpublished observations.
40. BRUCE, R. A., LOVEJOY, F. W., JR., YU, P. N. G. and MCDOWELL, M. Evaluation and significance of physical fitness for moderate work. *Arch. Indust. Hyg.*, 4: 236, 1951.
41. WILKINS, R. W., FREIS, E. D. and STANTON, J. R. The treatment of essential hypertension with veratrum viride and with dihydroergocornine. (In preparation.) Quoted by Wilkins, R. W. et al. The hemodynamic effects of sympathectomy in essential hypertension. *Ann. Int. Med.*, 30: 291, 1949.
42. JOSEPHS, I. L. Therapy of hypertension. The use of veratrum viride alone and combined with certain dihydrogenated alkaloids of ergot. *Ann. West. Med. & Surg.*, 4: 789, 1950.
43. KINSEY, D. and SMITHWICK, R. H. Unpublished observations. Quoted by Wilkins, R. W. et al. The hemodynamic effects of sympathectomy in essential hypertension. *Ann. Int. Med.*, 30: 291, 1949.

The Control of Hypertension with 1-Hydrazinophthalazine (Apresoline)*

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THE treatment of hypertension has as its goal prevention of the well known complications of elevated arterial pressure. These complications are thought to be due chiefly to sustained elevated pressure and not to the underlying cause of the increased peripheral resistance. Consequently, the ideal regimen of therapy should be one which will maintain arterial pressure within normal limits. Only when control of the pressure is impossible should it be necessary to rely on supportive therapy.

Satisfactory control of arterial pressure in some patients has been achieved by various methods during the past few years, and a favorable effect on morbidity and mortality has been observed. However, the difficulties in maintaining drastic dietary restrictions or in carrying out rather extensive surgical procedures have led to an intensive search for simpler and more universally effective methods of treatment.

In 1949 preliminary studies by Gross, Druey and Meier[1] indicated that various phthalazine derivatives held promise as hypotensive agents. One of these compounds, 1-hydrazinophthalazine, was found to have minimal toxicity and maximal effects on blood pressure. In addition, studies by Reubi[2] and Moyer et al.[3] revealed an increase in renal blood flow in animals and humans given this compound. This fortuitous combination of peripheral and renal vasodilatation led to studies of the value of this drug in the treatment of hypertension.[4–7]

This article presents the results of the treatment of sixty-five hypertensive patients with 1-hydrazinophthalazine. These patients were studied at Vanderbilt University Hospital, Meharry Medical College and Thayer Veterans Administration Hospital.

METHODS

The majority of the patients reported here were studied on an outpatient basis. Those who were hospitalized during all or part of their course were treated in the same manner as the others. All patients with significant hypertension with symptoms who were seen by the authors were given the drug.

Patients were studied during a baseline period before medication was given. The average pre-treatment blood pressure was determined, and routine studies were carried out to evaluate the severity of vascular damage, the degree of renal involvement and, when possible, the etiology of the hypertension. The tests included electrocardiogram, chest x-ray, intravenous pyelograms, urinalysis and culture, serum non-protein nitrogen, phenolsulfonphthalein excretion, Fishberg concentration test and in some cases a benzodioxane test. In addition, baseline values for blood counts were obtained to serve as an index to possible future drug reactions.

Administration of 1-hydrazinophthalazine† was begun in doses of 50 mg. by mouth three or four times a day after the preliminary studies had been completed. This dose was gradually increased until a desired therapeutic effect was obtained or intolerance to the drug developed. Most patients took the medicine three times a day but schedules of every six or every four hours were used in some patients whose blood

† 1-Hydrazinophthalazine (apresoline®) was generously supplied by Ciba Pharmaceutical Products Inc.

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pressure did not fall satisfactorily on less frequent dosage.

During the period of administration of the drug periodic observations were made of the serum non-protein nitrogen, blood counts and urines. In addition, PSP excretion was estimated

TABLE I
EFFECT OF 1-HYDRAZINOPHTHALAZINE ON THE BLOOD PRESSURE OF HYPERTENSIVE PATIENTS

Change in Pressure	Essential Hypertension	"Renal" Hypertension	Malignant Hypertension	Post-sympathectomy	Total
Rise	1	0	0	0	1
No effect	7	6	1*	1	15
Decrease, 0 to 20 mm	2	2	1†	1	6
Decrease > 20 mm	31	1	4	1	37
Totals	41	9	6	3	59

* Terminal when drug started.
† Unable to tolerate more than 150 mg. per day.

at the peak of the effect on the blood pressure to determine whether there was any grossly demonstrable change in renal excretory function. In cases where the drug was discontinued laboratory tests were made until it was apparent that there was no toxic effect from the drug.

All blood pressure determinations were made after the patient had achieved a relatively basal state. Readings were taken at each visit with the patient reclining, sitting and standing to detect the presence or absence of postural hypotension. The disappearance of sound was taken as the diastolic pressure. All pressures recorded in this paper were taken in the sitting position.

RESULTS

Most hypertensive patients had a considerable drop in blood pressure when given this drug. (Table I.) Of fifty-nine patients who took the drug long enough for evaluation of its effect on the blood pressure thirty-seven (63 per cent) showed a drop in both systolic and diastolic pressures of more than 20 mm. Hg. An additional six (nine per cent) had a smaller but still definite drop. It is apparent, however, that there was a marked difference in the response of hypertension due to various causes. The various groups will be considered separately.

Essential Hypertension. Forty-one patients with essential hypertension were studied. (Table II.) These patients had varying degrees of severity of symptoms and duration of illness. None were in the malignant phase of the disease. Thirty-one of these patients had a drop in both systolic and diastolic pressures of 20 mm. Hg or more. The mean pre-treatment pressure for the entire group was 202/123. The mean pressure during therapy was 165/99. The arithmetical mean change in pressure was −37 mm. systolic pressure and −24 mm. diastolic pressure. The statistical

TABLE II
EFFECT OF 1-HYDRAZINOPHTHALAZINE ON THE BLOOD PRESSURE OF PATIENTS WITH ESSENTIAL HYPERTENSION

Age	Blood Pressure	
	Before	After
Males		
28	170/100	170/100
29	230/130	170/90
31	170/110	130/70
31	160/120	110/80
34	170/140	160/110
35	224/124	200/100
36	210/140	210/140
38	170/110	155/70
38	190/116	160/90
39	210/140	210/140
45	170/120	170/120
45	230/140	160/110
46	210/124	150/100
49	200/135	170/100
51	190/120	170/100
53	160/120	160/90
55	190/130	170/110
59	200/110	150/90
60	240/130	165/85
60	265/130	180/104
61	210/140	135/80
61	200/120	140/100
64	200/120	174/100
65	260/140	170/90
68	175/100	175/100
Females		
25	210/126	130/80
38	218/134	146/86
42	210/115	160/75
42	180/115	125/70
42	224/126	184/102
42	206/110	184/128
44	200/125	156/110
45	230/140	160/110
45	250/120	220/120
47	226/128	180/106
49	194/140	150/106
50	200/125	160/100
51	230/120	190/90
56	170/108	170/108
56	200/120	150/85
56	190/130	170/110

probability of this change occurring by chance is less than 1 in 10,000.

Of the thirty-one patients who had a definite drop in pressure fifteen failed to drop to normotensive levels. The others were kept within normal limits for periods of from four to twenty weeks. (Fig. 1.)

drop in blood pressure during the first few days of treatment. However, within two weeks the pressure had returned to pre-treatment levels. During therapy there was no change in renal excretory capacity as indicated by the serum NPN or by PSP excretion and Fishberg concentration tests.

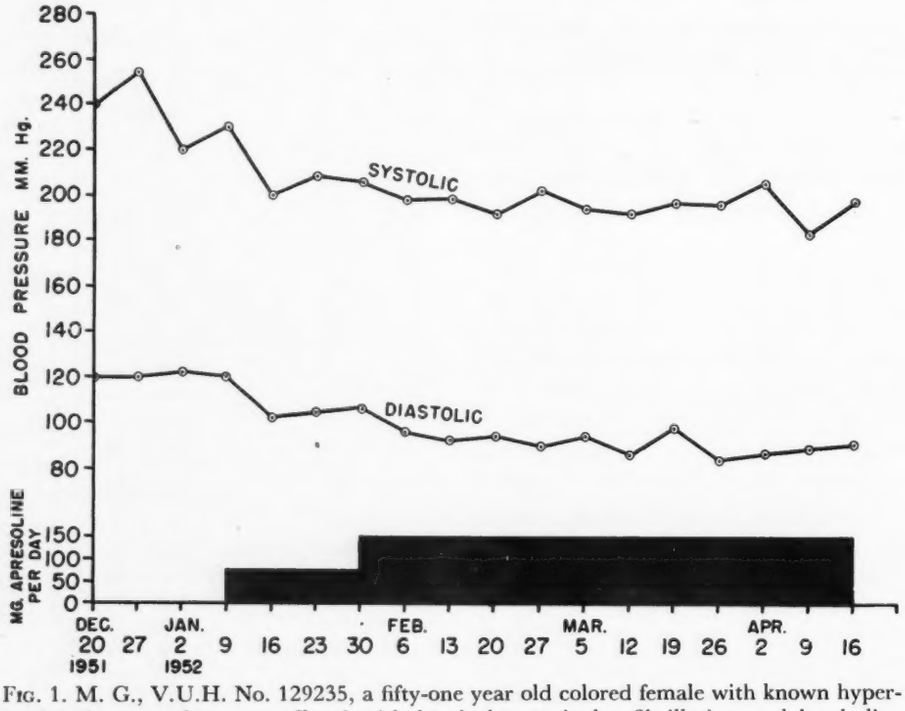

FIG. 1. M. G., V.U.H. No. 129235, a fifty-one year old colored female with known hypertension for several years, suffered with headache, auricular fibrillation and borderline congestive failure. PSP excretion was 60 per cent in one hour; no therapy other than 1-hydrazinophthalazine was administered; patient improved and is continuing drug.

Ten patients in this group had little or no response to the drug. In general, these patients had had hypertension for several years prior to therapy and showed a considerable degree of permanent vascular damage. Patients who had severe renal involvement and an elevated serum non-protein nitrogen were the least responsive to the drug.

Renal Hypertension. Nine patients were studied whose hypertension was believed to be of renal origin. (Table III.) None of these patients were in severe renal failure and none had malignant hypertension. Only one of these showed a drop in pressure of more than 20 mm. Hg. Seven showed no significant drop despite large doses of 1-hydrazinophthalazine. In one case, the pressure rose during treatment. The average blood pressure before treatment was 230/133. The average pressure during treatment was 225/130. This change is not statistically significant.

Two patients in this group had a moderate

Three patients in this group were given hexamethonium* in addition to 1-hydrazinophthalazine. The blood pressure response to combined therapy was variable but all showed a drop in renal function while on hexamethonium. Two of these patients had a prompt drop in pressure but in one case the drop was only temporary and the pressure returned to original levels despite continuing, intensive therapy.

Figure 2 outlines the course of the third patient in this group given combined therapy. He was given hexamethonium after his pressure had shown a moderate but inadequate fall with 1-hydrazinophthalazine alone. The pressure did not fall further when hexamethonium was added but the serum NPN rose from 50 mg. to 60 mg. per cent, and PSP excretion dropped from 44 per cent in two hours to 20 per cent in two hours. These changes reversed themselves

* Hexamethonium (bistrium®) was generously supplied by the Squibb Co.

when hexamethonium was stopped and 1-hydrazinophthalazine continued.

Malignant Hypertension. Six patients with malignant hypertension were studied. (Table IV.) The criteria for diagnosis of this condition were an elevated serum NPN, papilledema, albuminuria and hematuria. All were critically ill when first seen.

Excellent results were obtained in two patients. The blood pressures dropped to nearly normal levels and the albuminuria and papilledema improved. These patients were both seen early in the course of their illnesses and were able to take the drug without side effects.

Two patients died shortly after therapy was begun. One patient had a drop in blood pressure; one did not. It is impossible to evaluate properly the effect of the drug in these cases.

The remaining two patients were forced to discontinue therapy because of intolerance to the drug. One had shown a good response which was subsequently maintained with hexamethonium. The other stopped treatment after only three doses and evaluation is impossible.

Postsympathectomy. Three patients were studied who had previously been treated with sympathectomy without satisfactory results. (Table V.) All showed some drop in pressure when 1-hydrazinophthalazine was given. In one the pressure returned to normal levels and the patient is doing quite well. However, in the other two the pressure remains elevated. One has shown essentially no effect, even on 900 mg. of 1-hydrazinophthalazine a day. The other has shown a slight drop in pressure but no clinical improvement.

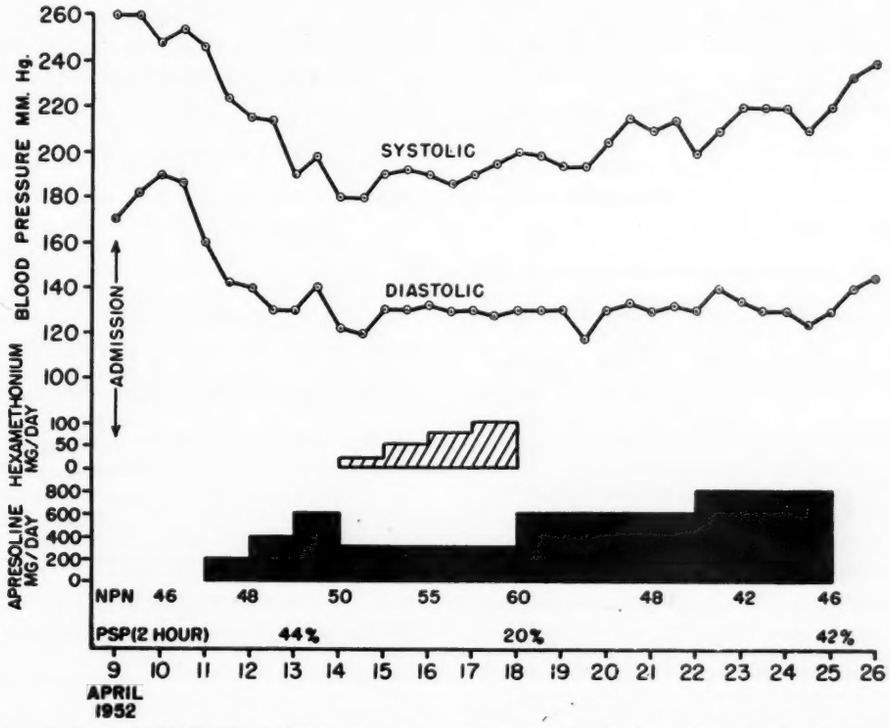

FIG. 2. J. S., V.U.H. No. 165848, a twenty-seven year old white male with chronic pyelonephritis. 1-Hydrazinophthalazine was given but discontinued because of side effects.

Side Effects. Of sixty-five patients placed on this drug thirty were able to take large doses without any significant side effects. The other patients developed various problems which are tabulated in Table VI. Ten patients were forced to discontinue the drug because of disagreeable side effects. The remaining twenty-five were able to continue the drug.

Patients who suffered from headache or vertigo could usually be relieved with antihistaminics but in several cases the relief was accompanied by a partial loss of blood pressure control. As a rule, patients suffering from headache who continued to take the drug gradually became more tolerant to the medication. A similar increase in tolerance was noted in patients complaining of nervousness and drowsiness. In the patients with the other side effects,

however, there was little demonstrable change in their reaction to the drug as they continued to take it.

COMMENTS

Our results indicate that 1-hydrazinophthalazine is an effective agent for the short-term control of blood pressure in certain cases of essential hypertension and malignant hypertension. It is also moderately effective in lowering the blood pressure of patients who have had sympathectomy but whose pressure has remained high after operation. In cases of so-called "renal hypertension," however, this compound has proven to be of little or no value. These results are similar to those reported by Schroeder.[4,7]

The mode of action of phthalazine derivatives on blood pressure is only partially understood. Freis[8] and Moyer et al.[3] have demonstrated that under certain conditions phthalazine derivatives inhibit the pressor action of nor-epinephrine and epinephrine. Antagonistic action has also been demonstrated against hypertensin,[7] sustained pressor substance,[9] serotonin[10] and pherentasin.[11] In addition, a direct central action on the hypothalamus or the medulla has been demonstrated by Gross et al.[1]

TABLE III
EFFECT OF 1-HYDRAZINOPHTHALAZINE ON THE BLOOD PRESSURE OF PATIENTS WITH HYPERTENSION OF "RENAL" ORIGIN

Patient	Blood Pressure		Comments
	Before	After	
A. H.	220/120	220/120	Chronic glomerulonephritis
E. M.	260/150	260/150	Pyelonephritis
J. W.	230/122	260/130	Pyelonephritis and lithiasis
E. H.	190/130	190/130	Probable chronic glomerulonephritis
E. K.	200/130	190/120	Polycystic kidneys
E. V.	240/130	240/130	Pyelonephritis
H. C.	190/110	190/110	Chronic glomerulonephritis
J. A.	260/140	250/140	Probable chronic glomerulonephritis
J. S.	290/170	220/130	Chronic pyelonephritis

TABLE IV
EFFECT OF 1-HYDRAZINOPHTHALAZINE ON THE BLOOD PRESSURE OF PATIENTS WITH MALIGNANT HYPERTENSION

Patient	Blood Pressure		Comments
	Before	After	
J. Mc	220/140	160/80	Died in uremia 10 days after start of therapy
B. B.	250/150	250/150	Died in uremia 6 days after start of therapy
M. P.	230/160	220/150	Forced to stop drug because of nausea and vomiting
F. H.	300/160	160/80	Greatly improved
E. D.	230/170	180/105	Greatly improved
H. Mc	290/150	170/95	Improved temporarily but forced to stop drug because of nausea and vomiting

TABLE V
EFFECT OF 1-HYDRAZINOPHTHALAZINE ON THE BLOOD PRESSURE OF PATIENTS PREVIOUSLY TREATED WITH SYMPATHECTOMY

Patient	Blood Pressure		Comments
	Before	After	
H. H.	185/135	180/130	250/150 before surgery; had transient lowering of pressure when first given drug
T. F.	160/120	120/80	200/150 before surgery; doing well now
B. T.	210/160	174/125	Unchanged by surgery; slightly improved but still severely symptomatic on present regimen

TABLE VI
SIDE EFFECTS NOTED DURING 1-HYDRAZINOPHTHALAZINE THERAPY

Effect	No.*	%	No. Who Stopped Drug
None	30	46	0
Headache	11	17	1
Tachycardia	11	17	1
Nausea	10	15	7
Vertigo	5	8	0
Drowsiness	5	8	1
Nervousness	3	5	0
Cytopenia (moderate)	2	3	2
Leukocytosis	2	3	0
Dermatitis	1	1.5	1

* The above totals exceed 100 per cent because the same patient showed more than one effect.

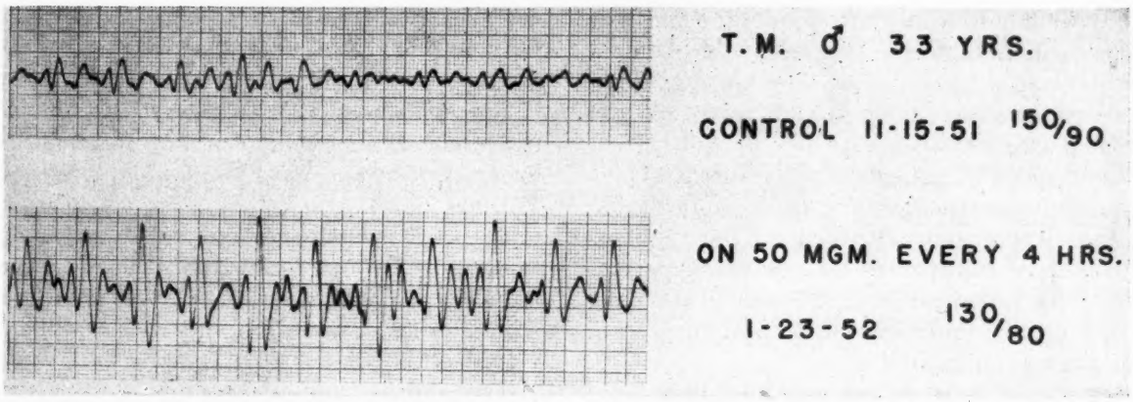

FIG. 3. T. M., a thirty-three year old white male, was admitted to Thayer Veterans Administration Hospital in November, 1951, complaining of easy fatiguability, exertional dyspnea and moderately severe frontal headaches. Admission blood pressure was 170/110 but this fell to 150/90 with hospital bed rest. The heart was slightly enlarged. The ballistocardiogram taken at this time exhibits complexes of poor amplitude and irregular, abnormal contour. With 1-hydrazinophthalazine (50 mg. every four hours) the blood pressure decreased to 130/80 where it has remained since discharge from the hospital. The patient feels much better and has an increased tolerance to work. The ballistocardiogram taken during therapy reveals a more normal contour with a marked increase in the I-J amplitudes indicating a greater early acceleration imparted to the ejected blood. The K-wave (associated with peripheral resistance) has fallen to its normal location below the base line.

The hypotensive effect is thought to be largely due to dilatation of the visceral vessels[3] although Walker et al.[12] have noted changes in the extremities which probably play a secondary but significant part. The change in pressure occurs slowly and suggests that the drug does not act directly on the blood vessels but instead on some pressor system. Schroeder[13] has suggested that inactivation of carbonyl groups is the basic change which takes place. In studying pherentasin isolated from the blood of hypertensive patients he found that a carbonyl group is essential for the prolonged pressor activity of this primary amine. Substances such as sulfhydryl-containing compounds which would inactivate this group had a definite depressor action. Hydrazine derivatives are known to be able to attack carbonyl groups, and Schroeder was able to block the pressor action of pherentasin with 1-hydrazinophthalazine and 1-hydrazino-4-methyl-phthalazine.

Meier[1] believes that the hypotensive response is central in origin and this concept is given support by the observation by Moyer et al.[3] that anesthesia markedly alters the reaction of renal blood flow to 1-hydrazinophthalazine. In all likelihood, both central and peripheral mechanisms are mediated.

Although there is a certain amount of adrenergic blocking by these compounds, the most significant pharmacologic actions are the increase in renal blood flow[2,3] and the inhibition of cerebral hormonal pressor substances.[10] These actions are both extremely desirable in the therapy of clinical hypertension. No other substance is known to have such an effect on the cerebral pressor substance which has been suggested by some to be the cause of persistent hypertension in patients who have had unsuccessful sympathectomy.[10]

Increased renal blood flow can be produced by pyrogen or by fever therapy but, as Reubi[2] has indicated, such treatment is rarely suitable for clinical use. The increase in renal blood flow by 1-hydrazinophthalazine is due to a decrease in resistance in the renal vascular bed.[3] No additional nephrons are activated and there is no increase in glomerular filtration rate or rate of tubular reabsorption of glucose. It is believed that the vascular bed of each nephron dilates and that vascular shunts do not play a part in the change.

This renal effect is quite different from that usually seen with drugs which lower blood pressure. It permits the use of 1-hydrazinophthalazine in situations in which other drugs are contraindicated. Even patients with renal impairment tolerate the drug well. In the patients reported in this paper no adverse effect on renal function was noted. The increase in blood flow, however, does not increase the renal function and there is no reason to expect therapy with this drug to reverse renal failure.

The failure of our patients with "renal hypertension" to respond to 1-hydrazinophthalazine confirms the reports of Schroeder.[4,7] The exact reason for this remains unknown but it is inter-

esting to note that this is so despite the fact that 1-hydrazinophthalazine prevents the pressor effect of hypertensin[7] and controls the blood pressure of dogs made hypertensive by the perinephritis technic.[14]

Our results in patients with persistent hypertension after sympathectomy are not as favorable as those reported by Schroeder.[4] Two patients out of three continue to have severe hypertension. Final judgment as to the value of this drug in this type of patient should be postponed until more cases can be studied.

Experimental work has indicated that 1-hydrazinophthalazine causes an increased cardiac output and tachycardia.[3] This occurs before the drop in peripheral resistance and is thought to be due either to a direct action on the heart or a reflex mechanism.[3] Clinically, tachycardia has been a common finding but certainly not a constant one. Cardiac output was measured in one of our patients by cardiac catheterization. Intravenous 1-hydrazinophthalazine caused a marked and rapid rise in cardiac output.

The effects of 1-hydrazinophthalazine on the ballistocardiogram have been investigated in our laboratory and compared with other hypotensive agents.[15] Although only intermediate in depressor ability, 1-hydrazinophthalazine proved capable of producing greater over-all improvement in ballistocardiographic contours than other drugs tested (hexamethonium, sodium amytal, veratrone,® regitine,® priscoline®). The I-J amplitude increased, as demonstrated in Figure 3. This is interpreted to indicate that the heart is able to eject blood more forcibly under the influence of 1-hydrazinophthalazine. Part of this can be attributed to decreased peripheral resistance (as demonstrated by the drop in the K-wave in Figure 3) but, in acute experiments, intravenous 1-hydrazinophthalazine causes these changes before the peripheral resistance drops, so other factors are undoubtedly involved.

These effects make it apparent that careful consideration must be given to the use of this drug in patients with congestive heart failure. However, no adverse effects have been noted in three patients with congestive failure in our series. Two have definitely improved. Schroeder has reported similar results.[7]

The headaches caused by 1-hydrazinophthalazine are thought to be due to histamine which accumulates because of the antihistaminase activity of the drug.[7] They can often be controlled with antihistaminics, if necessary, but in most cases the headaches become less severe as the drug is continued and they eventually disappear.

Patients who develop nausea and vomiting with this drug usually do not develop any tolerance to it and must discontinue treatment. This has been one of the most frequent practical problems in the clinical use of 1-hydrazinophthalazine. The only effective means we have found for overcoming this intolerance is to start with very small doses and increase the amount very slowly.

The gradual building up of drug dosage is also important in preventing a severe reaction to the new low arterial pressure. Most patients go through a period of weakness, lassitude and mild depression when their blood pressure first drops. This reaction seems to be more severe in those patients who have a rapid drop, and it is usually advantageous to lower the pressure gradually.

Overdosage with 1-hydrazinophthalazine is not a practical problem. Both in man and in experimental animals there is a "floor" below which the blood pressure will not drop despite increasing doses.[16] The limit of dosage is usually determined by the appearance of undesirable side effects and not by an exceedingly low blood pressure.

SUMMARY

1. The results of treatment of sixty-five hypertensive patients with 1-hydrazinophthalazine are presented.

2. Patients with essential hypertension or malignant hypertension responded favorably.

3. Patients with hypertension of the "renal" type showed an insignificant response.

4. Postsympathectomy patients with persistent hypertension had variable responses and judgment as to the value of the drug must be delayed until more cases are studied.

5. Undesirable side effects caused ten patients to discontinue the drug.

6. The pharmacology of 1-hydrazinophthalazine is discussed.

REFERENCES

1. Gross, F., J. Druey and Meier, R. A new group of depressor substances with a special type of effect. *Experientia*, 6: 19, 1950.
2. Reubi, F. C. Renal hyperemia induced in man by a new phthalazine derivative. *Proc. Soc. Exper. Biol. & Med.*, 73: 102, 1950.

3. Moyer, J. H., Handley, C. A. and Huggins, R. A. Some pharmacodynamic effects of 1-hydrazinophthalazine (C-5968) with particular reference to renal function and cardiovascular response. *J. Pharmacol. & Exper. Therap.*, 103: 368, 1951.
4. Schroeder, H. A. Effects of 1-hydrazinophthalazine in hypertension. *Circulation*, 5: 28, 1952.
5. Page, I. H. Treatment of essential and malignant hypertension. *J. A. M. A.*, 147: 1311, 1951.
6. Freis, E. D., Finnerty, F. A., Jr., Schnaper, H. W. and Johnson, R. L. The treatment of hypertension with hexamethonium. *Circulation*, 5: 20, 1952.
7. Schroeder, H. A. Control of hypertension by hexamethonium and 1-hydrazinophthalazine. *Arch. Int. Med.*, 89: 523, 1952.
8. Freis, E. D., Mackay, J. C. and Oliver, W. F. The effect of "sympatholytic" drugs on the cardiovascular responses to epinephrine and norepinephrine in man. *Circulation*, 3: 254, 1951.
9. Helmer, O. M. Cited by Schroeder.[7]
10. Taylor, R. D., Page, I. H. and Corcoran, A. C. A hormonal neurogenic vasopressor mechanism. *Arch. Int. Med.*, 88: 1, 1951.
11. Schroeder, H. A. Personal observations.[7]
12. Walker, H. A., Wilson, S. and Richardson, A. P. Effect of 1-hydrazinophthalazine (C-5968) on cardiovascular system of unanesthetized dogs. *Federation Proc.*, 9: 323, 1950.
13. Schroeder, H. A. Effects on hypertension of sulfhydryl and hydrazine compounds. *J. Clin. Investigation*, 30: 672, 1951.
14. Page, I. H. and McCubbin, J. Unpublished observations, cited by Taylor.[10]
15. Kory, R. C., Roehm, D. C. and Meneely, G. R. The ballistocardiographic response to "depressor" drugs. *Proc. Am. Federation Clin. Research, Am. J. Med.*, in press.
16. Craver, B. N. and Yonkman, F. F. Some pharmacological properties of 1-hydrazinophthalazine, a hypotensive agent. *Federation Proc.*, 9: 265, 1950.

Effect of Veriloid upon Renal Function When Administered in Hypotensive Doses to Patients with Arterial Hypertension*

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THE intimate relationship of hypertension and renal functional impairment makes it imperative to evaluate the effect of antihypertensive therapy upon renal function. Veriloid® a proprietary extract of Veratrum viride, has recently been introduced by Stutzman et al[1] and Wilkins et al.[2] as a hypotensive agent. Freis et al.[3] have presented limited data on the effect upon renal function of oral and intramuscular veratrone® and vertavis,® while Meilman[4] has presented similar data for protoveratrine.® There are no similar data available for veriloid. It was therefore desired to determine whether the kidney participated in the vascular response with a reduction in the filtration fraction and a return in the values for filtration rate and renal plasma flow toward normal, or whether the kidney failed to respond, with resultant further reduction in renal function due to the reduced hemodynamic pressure. If the latter were found to be true, it would then be necessary to determine if the increased uremia would jeopardize the patient, and whether the persistence of normotensive blood pressure would result in a later improvement in renal function. The present study has been designed to answer some of these questions.

PLAN OF EXPERIMENT

Seventeen male patients were studied; they ranged from twenty-six to sixty-three years of age and all had sustained arterial hypertension. Systolic blood pressures ranged from 160 to 260 and diastolic blood pressures ranged from 102 to 140 mm. Hg. The duration of known hypertension was from one to fifteen years, with an average of 6.8 years. These patients had been hospitalized or observed by the hypertension clinic and the levels of blood pressure were well documented. Evidence for other than primary arterial hypertension had been excluded. There were two Negroes in the group. The clinical data are summarized in Table 1.

Each patient was placed in a Fowler bed early on the morning of the study. A priming dose of para-aminohippurate (PAH) was injected and the sustaining solution started. The patient was then catheterized with a multieyed catheter. Urine collection periods were twenty minutes each, and the bladder was washed out after each collection with 15 ml. of sterile water followed by an injection of air. At least three control periods were obtained prior to the administration of veriloid. In most of the experiments the urine flow was maintained by a constant infusion of 5 per cent glucose solution injected intravenously through a separate needle

The veriloid solution was diluted so that each ml. contained approximately 1.32 μg. per kg. of body weight. This diluted solution was then injected into the running infusion at a rate no faster than ½ ml. per minute, during which time the blood pressure was taken at one-minute intervals. The injection was stopped after the administration of 4 ml. or at any time when there was an abrupt blood pressure fall, the pressure being allowed to stabilize for two minutes. Injection was then resumed at the same rate for another 3 ml. Usually at this time the blood pressure had dropped to the desired level, and this lowered blood pressure was maintained for a period of four to ten hours by the further injection of approximately 1 ml. every twenty minutes. If the blood pressure had

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not reached the desired level after the injection of 7 ml., more veriloid was injected at the same rate until the desired pressure was obtained. Actually, the rate of administration was much more cautious than indicated by this schedule, since the desired pressure level was reached only after an average of forty-eight minutes. (Table I.) The average hypotensive dose was 1.01 mg. and a subsequent average dose of 0.32 mg. per hour was required to maintain that level. An average of 55 mm. Hg fall in systolic pressure and 28 mm. Hg fall in diastolic pressure was obtained. Ampules of 1 per cent aqueous solution of ephedrine sulfate and of 1:1000 atropine sulfate were kept conveniently available to combat the possible complications of excessive hypotension and bradycardia, respectively. Blood specimens for the determination of serum creatinine and para-aminohippurate levels were drawn every thirty minutes.

The blood pressures were determined by a clinical sphygmomanometer applied to the brachial artery. Creatinine clearances were determined by the method of Brod and Sirota.[5] Para-aminohippurate was determined by the method of Smith et al.[6]

TABLE I

SUMMARY OF CLINICAL DATA

Pt.	Age	B.P. (Control)	Cardio-megaly	Eye* Grounds	Duration of A.H.† (yr.)	Hgb (gm./ 100 ml.)	Serum Creatinine (mg./ 100 ml.)	Protein-uria (gm./ 24 hr.)	Duration of Study		Time for B.P. Fall (min.)	Veriloid Required for B.P. Fall (mg.)	Total Veriloid Given, I.V. (mg.)
									Control (hr.)	Veriloid Admin. (hr.)			
Hut	63	259/140	+	III	3	13.4	4.5	0.75	1	10	45	0.92	4.20
Ra	61	250/140	0	II	1	13.0	2.9	1.3	1	10	70	1.06	3.68
Hu	47	230/150	+	III	9	16.2	3.0	0.2	4	6	45	1.25	1.44
Ma	51	220/128	0	II	6	15.8	1.8	0.9	1	8	65	1.32	4.80
Dr	42	205/138	+	I	9	16.2	1.6	3.6	1½	4½	20	0.95	2.72
Da	53	202/102	+	II	15	14.2	1.4	Trace	6	6	80	1.44	4.16
Pa	63	200/108	+	II	14	15.8	1.7	0.2	1	8	40	0.90	3.84
Ch	60	190/120	+	II	5	13.4	1.8	0.2	1	4	20	0.48	1.92
Ch	60	190/130	+	II	5	13.4	1.8	0.2	1	10	20	0.92	5.76
Wi	36	190/128	0	I	7	18.0	0.9	0	4	7	70	0.91	2.80
Me	42	184/114	0	I	7	15.8	1.6	0.2	1	10	75	1.32	4.40
Ro	58	178/126	+	II	1	15.4	2.3	Trace	1	10	60	1.28	3.76
Mi	55	176/108	0	II	2	12.85	1.1	Trace	2	10	35	0.76	1.74
Sc	57	176/116	+	III	10	14.6	2.5	0.6	1	4	30	0.50	1.76
Ir	26	170/120	0	0	7	18.8	0.8	Trace	1	10	24	0.64	3.20
Dr	42	170/108	+	I	9	16.2	1.8	2.4	4	8	30	1.09	3.28
Gr	47	170/110	0	III	5	17.3	1.6	0	2	10	90	1.57	4.00
Gl	56	158/96	0	II	1	15.8	1.4	0	1	10	30	0.84	3.20
Re	60	156/96	0	II	13	16.8	1.6	0.2	1	10	60	1.08	4.00
Av.	51.6	193/119	..	...	6.8	....	...	.....	..	8.16	48	1.01	3.40

* Keith-Wagener classification.
† Arterial hypertension.

RESULTS

In order to simplify tabulation the data for each patient were divided into three major periods. The first period was the control, the second period was the first four hours after the administration of veriloid, and the third period was the further duration of hypotension. The pulse rates, blood pressures and renal functions, determined for shorter periods, were averaged within each major period. These data are presented in Table II. The constancy of results within each period is shown by Figures 1 and 2.

As previously indicated, there was an average fall of 55 mm. Hg in the systolic pressure and of 28 mm. Hg in the diastolic pressure. The greater absolute fall in the systolic pressure was also relative, but not to the same degree, since the systolic fall averaged 28 per cent while the diastolic fall averaged 24 per cent. This did not represent the limit of hypotensive activity of the drug but was the approximate blood pressure level which had been predetermined as clinically advisable. Experience indicated that other levels could have been as easily obtained and maintained. In only one patient did the blood pressure initially drop faster than was expected, and a small amount of intravenous ephedrine was used to bring the pressure back to the desired level. It is interesting that this patient previously had had a bilateral sympathectomy (the only one in the series).

Concomitant with the fall in blood pressure the pulse rate fell from an average of 72 per

minute to an average of 64 per minute, which represented a fall of 10 per cent. In three patients the pulse rate dropped as low as 48. These three were given atropine sulfate intravenously although they had no associated symptoms or signs. The resultant cardiac acceleration had no effect upon the level of the blood pressure.

an increase after the first four hours, while the rest remained constant or actually increased throughout the hypotensive period. Correlated with this was the observation that the filtration fraction fell or remained unchanged in all but four of the studies. When the individual experiments were arranged in descending order of the

TABLE II

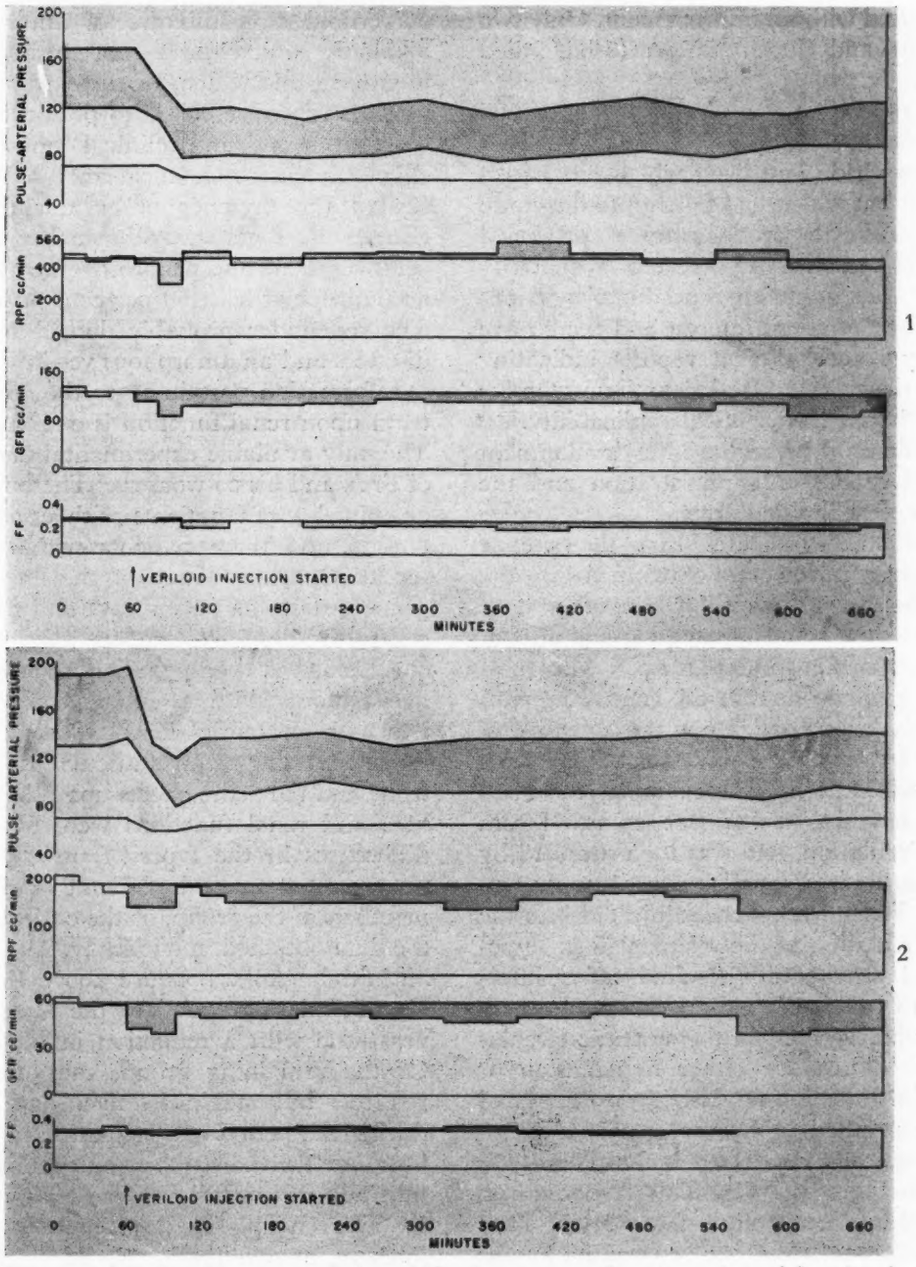
RESPONSE OF PULSE RATE, BLOOD PRESSURE AND RENAL FUNCTIONS TO INTRAVENOUS VERILOID

Pt.	Pulse Rate			Systolic B.P.			Diastolic B.P.			Glomerular Filtration Rate (ml./min.)			Renal Plasma Flow (ml./min.)			Filtration Fraction			Urine Flow (ml./min.)		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
Hut	75	60	63	259	175	177	140	97	98	17.2	12.8	16.3	51.3	40.3	52.8	.335	.318	.309	1.04	0.17	0.43
Ra	60	59	61	250	145	135	139	99	95	26.6	16.7	12.0	103	59.1	37.8	.258	.283	.317	1.83	1.01	0.89
Hu	84	68	70	229	157	158	150	118	121	15.5	12.8	11.8	68.4	52.3	43.3	.227	.245	.273	3.41	0.91	0.63
Ma	73	60	62	219	156	162	127	95	95	59.1	46.3	50.9	267	212	248	.221	.218	.205	3.98	1.95	0.81
Dr	75	61	..	207	141	...	138	101	...	87.9	43.9	.....	298	181	.....	.295	.243	....	5.00	0.57	....
Da	75	71	70	203	149	152	102	86	87	46.5	41.8	43.2	172	176	194	.270	.238	.223	3.02	0.24	2.10
Pa	68	58	61	200	139	159	107	82	93	69.2	54.3	39.1	226	156	128	.306	.348	.305	4.69	3.76	2.54
Ch	71	63	66	191	132	137	132	90	90	58.3	47.1	44.2	188	150	144	.310	.314	.307	2.49	2.28	1.59
Ch	71	64	..	188	136	...	118	92	...	63.6	58.7	.....	208	155	.....	.306	.379	....	0.71	0.96	....
Wi	88	79	78	188	152	148	127	109	108	56.8	49.0	58.9	212	256	288	.268	.191	.205	2.95	1.42	5.98
Mc	63	58	60	184	140	133	114	92	88	68.6	50.8	51.3	243	180	240	.282	.282	.214	1.31	1.12	0.81
Ro	73	71	70	178	131	129	126	92	95	45.8	40.7	39.4	141	161	164	.325	.253	.240	2.10	1.05	2.52
Mi	73	72	72	176	118	122	108	77	78	63.7	56.2	46.2	207	219	211	.308	.257	.219	0.38	1.28	0.35
Sc	60	55	..	175	144	...	115	87	...	39.4	36.6	.....	125	128	.....	.315	.286	....	3.11	2.27	....
Ir	72	62	60	170	123	120	120	84	83	124	106	105	455	448	454	.273	.237	.231	6.60	3.58	4.74
Dr	73	62	68	169	128	143	108	79	93	41.7	37.6	38.5	186	209	201	.224	.180	.192	0.68	0.25	0.34
Gr	69	64	60	169	130	127	111	84	77	40.1	39.4	42.8	188	223	282	.213	.177	.152	3.29	0.13	2.56
Gl	61	57	56	157	121	122	95	82	84	56.3	55.0	58.3	187	209	211	.301	.263	.276	4.24	4.86	3.69
Re	78	72	72	156	123	125	95	80	77	82.0	72.5	76.2	317	305	327	.259	.238	.233	6.00	3.21	3.63
Av.	72	64	66	193	139	141	119	91	91	56.0	46.2	45.8	202	186	202	.279	.261	.244	2.99	1.73	2.07

The initial fall in blood pressure was almost invariably accompanied by a reduction in the glomerular filtration rate which averaged 17 per cent and which then continued essentially at the same level. The average renal plasma flow showed a similar but smaller fall of eight per cent in the second period, but rose to control values in the third period. As would be expected, there were slight decrements in the filtration fraction of 8 and 10 per cent in the second and third periods, respectively. The average decrease in the urine flow was 45 per cent in the second period and 31 per cent of control values during the third period.

Examination of individual cases reveals that there was a persistent fall in the renal plasma flow in only six of the nineteen studies. Three showed an initial fall in the plasma flow, with

level of the control systolic blood pressure, it was found that every patient who responded with a falling renal plasma flow, a rising filtration fraction, or both, had an initial pressure of 185 mm. Hg or more, while none of the patients with initial systolic pressures below 185 mm. Hg demonstrated this response. Thus hypertensives with control systolic blood pressures of 185 or less responded predictably to the hypotensive effect of veriloid by a moderate fall in the glomerular filtration rate, a slight rise in the renal plasma flow, and a marked fall in the filtration fraction. There was only a slight depression of the rate of urine flow in this group. On the other hand, hypertensives with control pressures of 185 or more responded unpredictably: all showed a decrease in the filtration rate, but some showed a rise and



FIGS. 1 and 2. Graphic representation of blood pressure, pulse rate and renal functional changes in patients Ir (Fig. 1) and Ch (Fig. 2). The fall in the blood pressure and subsequent maintenance of constant levels are shown. In patient Ir, the slight increase in RPF associated with the slight decrease in GFR resulted in a fall in the filtration fraction. In patient Ch, the moderate fall in both RPF and GFR was accompanied by no change in the filtration fraction. Note: The horizontal unbroken lines carried through the figures for renal function represent the average control values.

others a fall in both the renal plasma flow and the filtration fraction, and the rate of urine flow was often markedly depressed by the hypotensive response.

No serious toxic effects were observed to follow the use of the drug. Ten patients manifested some nausea or mild vomiting. Four patients who were tested during periods of encephalopathy were continued with the oral administration of veriloid. Two of these showed marked clinical improvement in symptoms and in blood pressure level, one showed slight improvement and one showed no change. Four patients with hypertension alone were continued

on oral veriloid without improvement. Only two patients, Hut and Hu, are known to have died since the study.

COMMENTS

Veratrum viride is a drug which has had a long history but which had fallen into disrepute largely because the crude extracts produced unpredictable results. The recent availability of purified fractions with reproducible actions has stimulated renewed interest and there have been many recent clinical reports indicating that these drugs are effective antihypertensive agents which may have clinical applicability.[7–10] Major problems at present are the development of practical modes of administration and the delineation of toxic side effects.

Some evidence indicates that the site of pharmacologic action of veratrum is in the visceral afferent pathways,[11] while other data suggest that the site of hypotensive action is at or in the arteriolar musculature.[12] The most convincing evidence is that the central nervous system is the principal if not the sole site of action.[13,14] In the cross circulation experiments of Swiss and Maison,[14] for example, the head circulation of recipient dogs was separated from the body circulation, and was then supplied by blood from donor dogs. The nerve supply was left intact. When veriloid was injected into the systemic circulation of the recipient dog, hypotension and bradycardia resulted. After interference with the vagus, either by section or by atropinization, veriloid in the systemic circulation failed to produce either hypotension or bradycardia. Injection of veriloid into the head circulation resulted in hypotension in the isolated but neurally connected body. There was no associated bradycardia. This response was not affected by carotid sinus denervation. Thus the vagal afferents appear to be essential for the production of bradycardia, and may initiate an afferent stimulus to hypotension. The major mechanism for veratrum hypotension seems to originate in the central nervous system. This response is not dependent upon carotid sinus afferent stimulation. Recently, Swiss[15] and Fairbanks and Borison[16] have shown that the emetic effect is most probably a central action on a vomiting center, and that it is closely related to the hypotensive effect in terms of dosage. Krayer and Reiter[17] have demonstrated that the alkaloidal glycosides are far more effective than are the unesterified alkaloids.

Veriloid is a mixture of amorphous ester alkaloids which have not been completely identified, and which, by the extraction process used, is reproducible as to physical properties, biologic assay and clinical antihypertensive effect. Extensive chemical analysis has demonstrated the presence of germitrine and neogermitrine, together with smaller amounts of protoveratrine and neoprotoveratrine such as to account for at least 50 per cent of the potency. The remainder probably derives from various di-esters and an amorphous veratric ester.

Information pertaining to the effect of veratrum upon renal function is extremely limited. The only available experimental data are those of Freis and his co-workers.[3] These investigators examined seven patients with essential hypertension and three patients with chronic glomerulonephritis. Three of these received oral vertavis daily for seven days and the results of control studies were compared with those at the conclusion of therapy. The remaining seven, five patients with essential hypertension and two with chronic glomerulonephritis, were administered single intramuscular doses of veratrone and the acute effects upon the blood pressure and renal functions were observed. The differences in the types of patients and their management make it difficult to compare the members of the group, or the entire group, with the data obtained in our study. All patients had an initial systolic pressure above 180 mm. Hg. One failed to respond to the injected dose of veratrone with a reduction in blood pressure. Of the remaining group, the pressures were reduced but stable in five, and fluctuating during the period of observation in four. In all but one there was a significant drop in the filtration rate, with a return toward normal in six. The renal plasma flow in most cases dropped initially, then returned to above control levels, and the filtration fraction was decreased in all but one case. The urine flow was significantly reduced after the drug administration in all cases, even when the clearance values for inulin or mannitol and PAH were within normal limits.

Meilman[4] performed inulin and PAH studies forty times on thirty-five patients with hypertension of varied etiology before and after the administration of protoveratrine. No experimental data are presented in his preliminary reports. "In ten studies after single intravenous injections of protoveratrine, a moderate to

marked fall in GFR and a lesser fall in ERPF usually occurred during the most marked blood pressure fall; both functions recovered toward, but not above control levels as the blood pressure rose to former levels." In order to avoid changing blood pressure levels, further studies were performed during a continuous infusion of protoveratrine which maintained the blood pressure at a steady low level for two to four hours. "These studies demonstrate that GFR usually approaches or reaches control levels 1–2 hours after the first lowering of blood pressure, while ERPF reaches or exceeds control values in this time. These observations are consistent with the hypothesis that the kidney is capable of undergoing vasodilatation following the administration of protoveratrine. The vasodilatation is accompanied by a marked decrease in the resistance of the kidney." Recently, Meilman[18] studied the antidiuresis caused by veratrum. He found that, unlike pituitary antidiuretic hormone, veratrum causes marked sodium and chloride retention, with a minimal effect upon potassium excretion. This electrolyte-retaining effect seems to persist longer than does the antidiuretic effect.

The data obtained in this study conform closely to those reported previously. In most cases there was a moderate reduction in glomerular filtration rate which was probably the result of two processes, first the reduction in hemodynamic pressure and, second, a reduction in the renal resistance due to relaxation of efferent arterioles. The latter mechanism is suggested by the increased renal plasma flow and especially by the fall in the filtration fraction. Four patients with advanced hypertension, as indicated by the level of the control systolic pressure, responded to the drug-induced hypotension by a marked fall in the filtration rate, a similar fall in the renal plasma flow, and a significant rise in the filtration fraction. Initially it was believed that this response represented the result of reduced hemodynamic pressure upon glomeruli anatomically unable to respond to vasodilatory stimuli because of advanced damage. However, examination of this group demonstrates that instead of being passively hemodynamic, there must have also been an active efferent arteriolar response, indicated by the rising filtration fraction. Apparently, while the less severely hypertensive individuals had a renal vasodilatory response, about one-half of the severely hypertensive individuals responded to the systemic hypotensive reaction caused by the veriloid with increased efferent arteriolar spasm. In no case did the reduction in filtration rate appear sufficient to jeopardize the individual by causing seriously increased azotemia. However, the extreme antidiuresis, especially in the more severely hypertensive patients, would probably result in increased back-diffusion of urea and possibly increased tubular reabsorption of other substances unless normal diuresis was resumed.

The significance of the antidiuresis observed is extremely difficult to assess. The free flow of urine during the control periods could be the result of water priming. Undoubtedly, the initial hypotensive response resulted in a reduced urine flow. However, the later failure of the urine flow to reach pre-treatment levels could be because the same rate of hydration was not maintained, or because of the normal afternoon reduction in urine flow, as well as the result of a persistent drug antidiuresis.

Clinically, it is possible with veriloid administered intravenously to lower blood pressure to almost any desired level and to maintain it at that level. To do this, however, requires constant attendance by an adequately trained individual, and intravenous veriloid can therefore be used only for short periods of time. The greatest field of usefulness is probably in hypertensive and eclamptic crises. The recent introduction of an intramuscular product may make it possible to treat a larger group of hypertensive patients on a maintenance basis. Toxic effects are minimal when the drug is administered slowly, as directed, and when an indwelling catheter is inserted into the bladder and urine flow is constantly observed to insure that the pronounced antidiuresis is not followed by anuria. The family should be warned of the possibility of cerebral and coronary thrombotic episodes which may result from the reduction of blood pressure, although no such episode was observed in this series. Other toxic side effects, such as substernal burning, a sense of warmth, hiccups, nausea and vomiting may interfere with administration of the drug. None of these is serious although the vomiting may be very distressing. Pharmacologic data[15,16] indicate that it is impossible at present to separate the emetic and hypotensive effects, and that emesis may be expected in a large proportion of patients. Large doses of phenobarbital are often effective in reducing this complication but

obviously cannot be used on a maintenance basis.

SUMMARY AND CONCLUSIONS

1. Veriloid, an extract of Veratrum viride, was administered intravenously nineteen times to seventeen patients, producing a stable hypotensive effect for periods of four to ten hours. No serious toxic side effects were observed in this group other than nausea and vomiting in slightly more than one-half of the patients.

2. Intravenously administered Veratrum viride consistently lowered the blood pressure in human hypertensive subjects. All patients responded, the average fall in the systolic pressure being 28 per cent, in the diastolic pressure 24 per cent. A concomitant 10 per cent slowing in the pulse rate was also observed.

3. In almost all individuals there was a moderate reduction in the glomerular filtration rate, an increase or maintenance of the renal plasma flow, and a resultant reduction in the filtration fraction. A profound antidiuresis observed during the first four hours tended to be reduced during the subsequent period but was not completely eliminated at the end of ten hours.

4. The renal hemodynamic changes seem to indicate that the renal arterioles participate in the general reduction in arteriolar resistance produced in response to the administration of veriloid.

5. A small group of patients, all of whom had initial systolic pressures above 185 mm. Hg, exhibited a marked fall in the glomerular filtration rate and renal plasma flow and a moderate increase in the filtration fraction after administration of the drug. It is believed that these patients actively responded to the reduction in systemic blood pressure by a further renal hypertensive response, i.e., further efferent arteriolar constriction as indicated by an increased filtration fraction. These patients also failed to show reversal of the antidiuretic effect of the drug even after ten hours.

6. Veriloid is a promising antihypertensive agent which generally but not invariably results in the return of renal hemodynamic mechanisms toward normal. This is accompanied by a moderate reduction in filtration rate which should not seriously increase the degree of uremia. However, in a few patients the reduction of function, coupled with profound antidiuresis, may be detrimental if continued for a prolonged period.

REFERENCES

1. Stutzman, J. W., Maison, G. L. and Kusserow, G. W. Veriloid, a new hypotensive extract of veratrum viride. *Proc. Soc. Exper. Biol. & Med.*, 71: 725, 1949.
2. Wilkins, R. W., Stanton, J. R. and Freis, E. D. Essential hypertension. Therapeutic trial of veriloid, a new extract of veratrum viride. *Proc. Soc. Exper. Biol. & Med.*, 72: 302, 1949.
3. Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H. and Wilkins, R. W. The hemodynamic effects of hypotensive drugs in man. I. Veratrum viride. *J. Clin. Investigation*, 28: 353, 1949.
4. Meilman, E. Action of protoveratrine on renal function in hypertension. *J. Clin. Investigation*, 30: 659, 1951.
5. Brod, J. and Sirota, J. H. The renal clearance of endogenous "creatinine" in man. *J. Clin. Investigation*, 27: 645, 1948.
6. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J. Clin. Investigation*, 24: 388, 1945.
7. Hite, W. K. Hypertension and veratrum viride. A Preliminary study. *Illinois M. J.*, 90: 336, 1946.
8. Freis, E. D. and Stanton, J. R. A clinical evaluation of veratrum viride in the treatment of essential hypertension. *Am. Heart J.*, 36: 723, 1948.
9. Wilkins, R. W. Veratrum viride and essential hypertension. *New England J. Med.*, 242: 535, 1950.
10. Stearns, N. S. and Ellis, L. B. Acute effects of intravenous administration of a preparation of veratrum viride in patients with severe forms of hypertensive disease. *New England J. Med.*, 246: 397, 1952.
11. Daws, G. S. Studies on veratrum alkaloids. VII. Receptor areas in the coronary arteries and elsewhere as revealed by the use of veratridine. *J. Pharmacol. & Exper. Therap.*, 89: 325, 1947.
12. Willson, J. R. and Smith, R. G. The peripheral circulatory action of veratrum viride. *J. Pharmacol. & Exper. Therap.*, 79: 208, 1943.
13. Moe, G. K., Bassett, D. L. and Krayer, O. Studies on veratrum alkaloids. V. The effect of veratridine and cervine upon the circulation of anesthetized dogs, with special reference to arterial flow. *J. Pharmacol. & Exper. Therap.*, 80: 272, 1944.
14. Swiss, E. D. and Maison, G. L. The site of cardiovascular action of veratrum derivatives. *J. Pharmacol. & Exper. Therap.*, 105: 87, 1952.
15. Swiss, E. D. The emetic properties of veratrum derivatives. *J. Pharmacol. & Exper. Therap.*, 104: 76, 1952.
16. Fairbanks, V. F. and Borison, H. L. Studies on the emetic action of veratrum alkaloids in cats. *J. Pharmacol. & Exper. Therap.*, 103: 343, 1951.
17. Krayer, O. and Reiter, M. Studies on veratrum alkaloids. XI. Jervine and pseudojervine, antagonists to the cardioaccelerator action of epinephrine and of accelerans stimulation. *Arch. internat. de pharmacodyn. et de thérap.*, 81: 409, 1950.
18. Meilman, E. The mechanism of protoveratrine-induced oliguria. *J. Clin. Investigation*, 31: 649, 1952.

Malignant Hypertension and Hypertensive Encephalopathy*

Cerebral Hemodynamic Studies and Therapeutic Response to Continuous Infusion of Intravenous Veriloid

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THE hypotensive effect of *Veratrum viride* has been known, at least, since 1874.[1] However, because of the poor standardization and undesirable effects resulting from the large doses employed[2] at that time, the drug fell into disrepute.[3] Due largely to the enthusiasm of Wilkins, Freis, Stanton and their associates,[4–7] the use of semi-purified extracts of *Veratrum viride* has been revived for the treatment of hypertension. Despite more accurate biologic standardization today, when these extracts are given orally the effective dosage has been difficult to regulate, and the reported beneficial results are controversial.[4,6,8,9] Frequently, long periods of time are necessary to determine the amount of drug required wherein a significant hypotensive response is obtained which is free of nausea and vomiting. Even then, the hypotensive response is variable and unpredictable.[8,9] Therefore, in patients exhibiting hypertensive crises in whom immediate reduction in blood pressure seems imperative, the use of these orally administered extracts is of limited value. The purpose of the following paper is to report some clinical and pharmacologic observations[10] on continuous infusion of intravenous veriloid,®† a chemically and biologically standardized extract of *Veratrum viride*. This agent has proven to be a consistent and dependable short-term hypotensive agent when administered intravenously although the incidence of side reactions is quite high. No attempt has been made at long-term evaluation. The cerebral blood flow and cerebral metabolic effects of reduction in blood pressure by this means were evaluated in ten patients in the series.

† Supplied through the courtesy of Riker Laboratories, Inc.

METHODS AND MATERIAL

Twenty-seven patients with severe hypertension, most of whom exhibited encephalopathy, are the basis of the present report. In twenty-two patients the etiology of the hypertension was unknown. Five had chronic glomerular nephritis. Measurements of pulse rate, respiratory rate and auscultatory blood pressure were taken during a two-hour control period and repeatedly during the course of each study. The dose of intravenous nor-epinephrine which would raise the mean blood pressure 20 mm. of mercury was established in six of the less ill patients. Cerebral blood flow determinations employing the nitrous oxide method[11] were carried out before and after intravenous veriloid in ten patients chosen at random. Only six of these presented encephalopathic manifestations and two (J. W., E. W.) exhibited azotemia. The blood pressures were carried to lower levels in these ten patients than in the series as a whole in order to obtain maximum changes in cerebral hemodynamics if they were to develop. This was possible because these patients were observed more closely by the investigative team

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than were the remainder of the patients. Therefore, a depression of the blood pressure to more critical levels was feasible.

After suitable control studies were completed in each of the twenty-seven patients, intravenous veriloid was administered. Initially, 1 μg. /kg./body weight/minute was given for ten minutes as a priming dose. This was repeated or was followed by a sustaining infusion, depending on the response of the blood pressure. However, it was soon observed that this method for administering the priming dose and thus establishing the desired therapeutic response was too rapid. The optimal hypotensive response was frequently passed, resulting in an excessive depression of blood pressure, bradycardia and vomiting after a three to ten-minute delay period. As a result, the same priming dose of the drug was subsequently given more slowly, usually over a twenty to thirty-minute period. In a few patients it was necessary to repeat the priming dose, at least in part, before adequate reduction in blood pressure was obtained. After the priming dose was completed and the desired blood pressure obtained, the patient was placed on sustaining infusion containing 3.6 mg. of veriloid per L. of 5 per cent glucose or 0.85 per cent saline. The rate of infusion varied between 10 and 100 drops (1.8 to 18 μg.) per minute, depending on the hypotensive response. Regulation of the rate of infusion required constant supervision. Blood pressure determinations were made every two minutes during the first thirty minutes and then every five minutes during the remainder of the stabilizing period. This required about one to two hours. After the stabilizing period blood pressures were taken every fifteen minutes to one-half hour as long as the infusion was continued. An attempt was made not to depress the blood pressure below 150 mm. mercury systolic and 100 diastolic. If nausea, vomiting or hiccoughs developed, the rate of infusion was decreased regardless of the blood pressure. At the same time that the veriloid infusion was set up, a similar one was prepared containing nor-epinephrine (4 mg./1,000 cc.) for immediate intravenous administration in case the hypotension at any time became excessive. This is an important precaution.

In the ten patients in whom cerebral blood flow studies were done, the blood pressure was stabilized at the desired level for thirty minutes to one hour. Then the cerebral blood flow studies were repeated. In order to evaluate the effect of the bradycardia on cerebral blood flow four patients were given atropine sulfate (1 mg.) intravenously. After the pulse rate had returned to the control value and appeared stabilized (thirty minutes or more after previous cerebral blood flow study), a third cerebral blood flow determination was done.

The ten patients (Group 2), in whom cerebral blood flow studies were conducted, received veriloid for only two to six hours. In the remaining seventeen patients (Group 1) veriloid was continued for varying periods of time depending on drug response and the severity of undesirable reactions. The maximum was ninety-six hours in three patients. In those patients in whom the response to a given dose of nor-epinephrine had been evaluated during the control studies, the same dose was repeated at varying intervals during intravenous veriloid therapy. The effects of atropine on the pulse rate, blood pressure and nausea and vomiting were also frequently evaluated.

RESULTS

The clinical response to intravenous veriloid given to the seventeen patients (Group 1) on whom cerebral blood flow studies were not done is summarized in Table 1.

The blood pressure decreased in every instance whether or not there was associated renal disease. This was not always accompanied by bradycardia, indicating that bradycardia is not necessary to obtain a reduction in blood pressure. However, the mean pulse rate for the group decreased from 88 to 69 which was statistically significant ($p < 0.01$). In some instances the dosage necessary for maintaining a steady hypotensive response varied from time to time during the course of intravenous therapy. Usually, however, after the rate of infusion was established little alteration was required. There was no evidence of tachyphylaxis. Intermittent nausea, epigastric burning and salivation occurred at some time in nearly all patients during the course of intravenous drug administration. Nausea was not recorded in Table 1 unless it was quite marked. In addition, vomiting occurred in four patients. This was preceded by epigastric burning or hiccoughing. Atropine appeared to improve the nausea and vomiting but did not completely arrest it or prevent it. Discontinuance of intravenous therapy became necessary after twenty-four hours in the four patients noted above because of pernicious

vomiting and/or severe hiccoughing. One patient who was in extremis on admission died after eighteen hours of therapy. In the remaining patients the drug was continued forty-eight hours in five, seventy-two hours in four and ninety-six hours in three. Interestingly enough, three patients who had extreme headache associated with pernicious vomiting prior to admission were relieved of both the headache and the vomiting during and after intravenous drug therapy. Eight additional patients showed definite evidence of improvement of their encephalopathic manifestations. Of the seventeen patients in the group, fourteen complained of feeling cold and weak concurrently with the drop in blood pressure. Frequently, after the pressure was depressed for twelve to eighteen hours, the patients became very restless and some degree of sedation and/or temporary ambulation became necessary.

Four patients (Nos. 5, 9, 10 and 16) were in coma on admission to the hospital. Two of them were conscious within forty-eight hours, responding to questions. However, one of the patients died eighteen hours after admission and the fourth (No. 16) showed no improvement during ninety-six hours of veriloid therapy although his blood pressure was markedly reduced. His blood urea nitrogen rose progressively from 64 mg. per cent to 200 mg. per cent and he died one week later.

After the drug was discontinued the blood pressure remained below control values in most instances for three days to one week. There was a direct relationship between the duration of intravenous veriloid therapy and the length of time the blood pressure remained depressed after the veriloid was discontinued. Following the course of intravenous therapy, the patients were started on some type of oral medication (hexamethonium, 1-hydrazinophthalazine, veriloid or anatensol). Because of recurrent encephalopathic manifestations, repeated courses of intravenous therapy were used in a number of instances with a hypotensive response which was quite similar to the original one.

Intravenous nor-epinephrine was not blocked by veriloid and is therefore effective in counteracting the hypotensive effect of veriloid. Typical experiments are seen in Figure 1. Since the effect of nor-epinephrine* is only transient, continuous infusion is necessary if it is to be used for this purpose. Atropine blocked the bradycardia quite effectively whenever it developed during and following the administration of

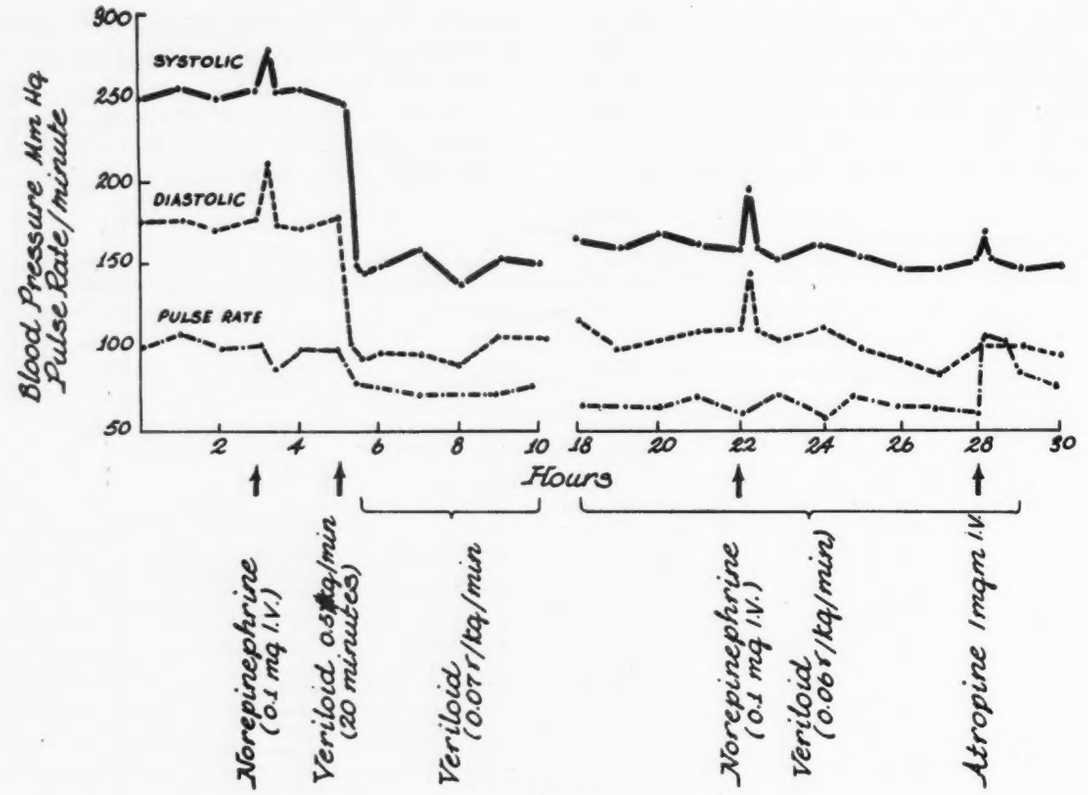
* Made up into a solution of 4 mg./L. of fluid.

TABLE 1

BLOOD PRESSURE AND SYMPTOMATIC RESPONSE TO CONTINUOUS INFUSIONS OF INTRAVENOUS VERILOID

Patient	Age	Known Duration (yr.)	Diagnosis	Pulse Rate		Blood Pressure			Side Reactions	Infusion Period (hr.)	Symptomatic Improvement (Encephalopathy)
				Control	During Infusion of Veriloid	Control Mean	During Veriloid Infusion				
							Mean	Range			
1	42	10	CN*	77	50	210/140	156/104	180/120—130/80	None	72	++
2	24	8	HCVD†	66	44	260/150	155/90	170/100—130/72	None	48	++
3	36	7	HCVD	82	80	300/210	180/125	200/140—150/110	Weakness	96	+++
4	51	2	HCVD	100	60	290/160	140/120	160/130—130/108	Hiccough, vomiting	24	+
5	28	13	CN	107	108	224/162	160/110	196/140—110/80	Restless	48	+++
6	48	1	HCVD	120	100	230/164	150/90	160/108—138/80	Dizzy, weak, nausea	48	+++
7	52	10	HCVD	80	64	248/130	162/90	180/104—148/82	Dizzy	48	+++
8	33	6	CN	90	70	190/120	110/66	130/100—90/58	Vomiting	24	++
9	29	6	CN	80	64	220/160	130/95	150/108—110/90	None	18	Patient died
10	27	4	HCVD	104	70	265/170	155/105	170/115—130/100	Vomiting	72	+++
11	60	7	HCVD	84	70	235/150	170/110	190/120—135/90	Nausea	72	+++
12	55	0.5	CN	100	50	225/145	180/130	200/140—170/120	None	96	+
13	48	0.3	HCVD	72	58	310/220	240/160	260/180—200/130	Weakness, hiccough	48	0
14	49	1	HCVD	84	76	200/140	130/100	158/115—120/80	Vomiting	24	0
15	53	2	HCVD	80	86	190/125	130/110	170/120—110/98	Hiccough, nausea	72	++
16	56	1	HCVD	76	72	240/162	150/100	170/110—140/96	None	96	0
17	54	1	HCVD	90	56	300/210	158/110	200/130—110/90	Hiccough, weakness	24	+++
Mean	44	4.7		88	69‡	243/159	156‡/107‡			55	

* CN—Chronic nephritis
† HCVD—Hypertensive cardiovascular disease
‡ Statistically significant change from control values ($p < 0.01$)



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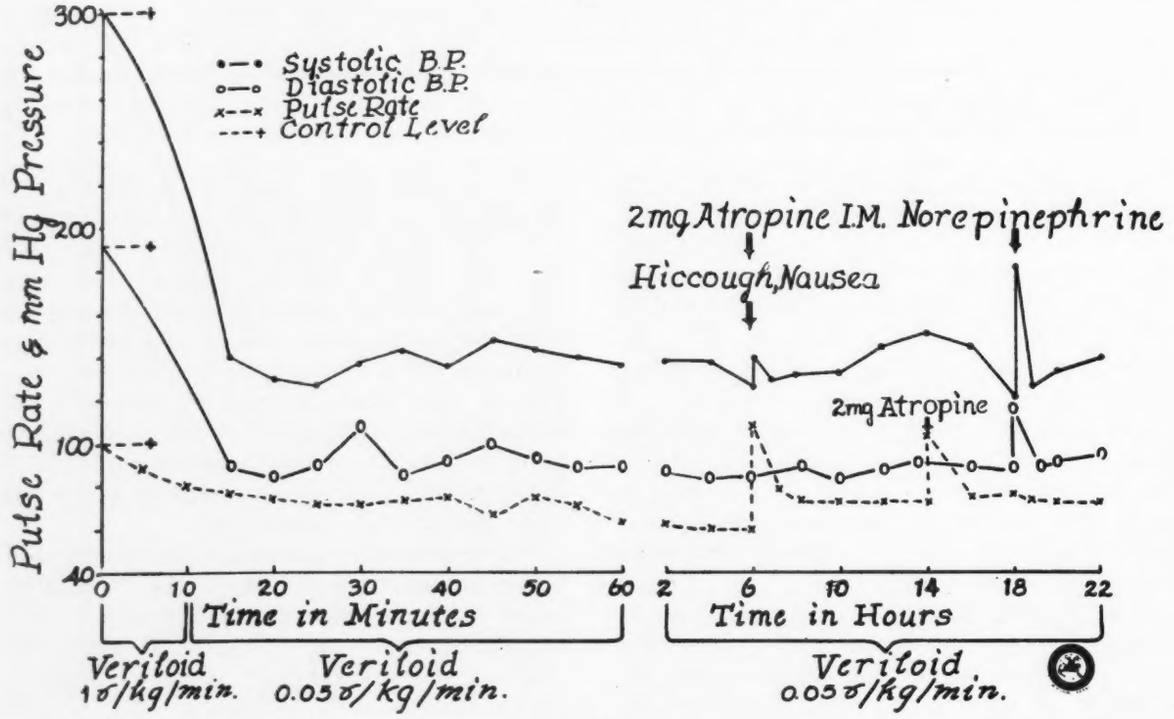

1B

FIG. 1. A, shows a typical response to intravenous veriloid.® The pulse rate and the systolic and diastolic pressure all decrease concurrently. Atropine blocks the bradycardia but displays only an insignificant and transient effect on blood pressure. The blood pressure response to a single dose of intravenous nor-epinephrine is just as marked after and during veriloid administration as it is during the control study. B, this is another patient showing prompt and adequate response to veriloid.

veriloid. Immediately after atropine the pulse rate usually increased above normal and then slowly dropped off to near the control ranges, but after thirty minutes to one hour bradycardia again developed. This bradycardia could repeatedly be blocked by atropine which was arrest. The electrocardiogram showed an auriculoventricular dissociation with marked bradycardia. Artificial respiration was given and the hypotension was reversed with ephedrine and nor-epinephrine. The bradycardia and A-V dissociation were corrected with atropine.

TABLE II

CLINIC SUMMARY AND BLOOD PRESSURE RESPONSE

Patient	Sex and Age	Diagnosis	Duration of Disease	Hematocrit	Respiratory Rate		Blood Pressure		Reactions
					Control	After Intravenous Veriloid	Control	After Intravenous Veriloid	
J. L.	F, 41	HVD*	1 yr.	44	22	16	180/104	133/81	None
A. S.	F, 41	HVD	4 yr.	37	20	18	206/133	150/110	Vomited
A. R.	F, 49	HVD	4 yr.	40	22	28	240/160	156/114	Nausea, hyperventilation during second CBF; relief of severe headache
R. T.	F, 45	HVD, CVA† (old)	10 yr.	35	16	..	250/140	130/90	None
A. H.	M, 28	HCVD‡	6 mo.	30	18	24	250/180	120/110	None
O. G.	F, 44	HCVD, CF§	2 yr.	34	..	..	236/140	150/106	Relief of severe headache
J. H.	M, 33	HVD	1 yr.	40	18	10	250/175	108/78	None
J. W.	M, 52	HCVD	10 yr.	30	20	20	204/130	140/100	Hiccoughs, nausea, vomiting
E. W.	M, 48	HCVD	4 yr.	38	26	30	250/150	150/100	Nausea, vomited
J. A.**	M, 34	HCVD	1 yr.	49	20	14	210/135	100/70	Severe hypotensive response prior to second CBF
Mean	42		3yr., 8mo.	38	20	20	228/145	134/96††	

* HVD—Hypertensive vascular disease
† CVA—Cerebrovascular accident
‡ HCVD—Hypertensive cardiovascular disease
§ CF—Cardiac failure
** Patient developed marked delayed hypotensive response.
†† Statistically significant change from control values ($p < 0.01$).

usually followed by a slight and transient rise in blood pressure. (Fig. 1A and B.)

A clinical summary of the patients on whom cerebral blood flow studies (Group 2) were done is found in Table II and cerebral hemodynamic studies are recorded in Table III.

The cardiovascular and hypotensive responses were quite similar to the patients in group 1. Apparently because the priming dose was given too rapidly* (ten minutes) and the blood pressure depressed too greatly, one patient (J. A.) developed vascular collapse and respiratory Recovery was uneventful but, needless to say, the priming dose of veriloid was administered more slowly and with more caution after this experience.

Except for the patient cited above, there was no evidence of respiratory depression and no significant alterations of pulmonary gas exchange as represented in arterial O_2 and CO_2 studies. (Table III.) The oxygen content in the blood coming from the brain was decreased an average of 2 volumes per cent which is significant ($p = 0.04$). This resulted in an increase of the mean cerebral A-V O_2 difference from 5.2 to 6.9 volumes per cent ($p = 0.02$). Associated with a significant decrease in cerebrovascular

* The rate of administration of the priming dose currently advised is considerably slower than that used in this patient. (Fig. 1A.)

resistance from 3.2 to 2.3 ($p = 0.04$), cerebral blood flow was only slightly decreased in the presence of a 24 per cent fall in systolic ($p < 0.01$) and a 30 per cent drop in diastolic ($p < 0.01$) blood pressure. Despite the greater cerebral uptake of oxygen per unit volume of blood, the $CMRO_2$ was without significant change when calculated from a cerebral blood flow which was lowered but within the normal range of variation ($p = 0.25$). In most of the individual patients showing a rather sharp reduction in cerebral blood flow the blood pressure was depressed excessively (A. H., J. H., J. A.). Atropine, although it increased the pulse rate, did not appear to affect the cerebral blood flow after veriloid. (Table III.) The cerebral hemodynamic studies are graphically summarized in Figure 2.

TABLE III

CEREBRAL HEMODYNAMIC EFFECT OF INTRAVENOUS VERILOID

Patient	Arterial				Venous				A-V O_2		CBF			CM-RO_2		MBP		CVR		Pulse Rate		
	CO_2 Vol. %		O_2 Vol. %		CO_2 Vol. %		O_2 Vol. %															
	C	V	C	V	C	V	C	V	C	V	C	V	A	C	V	C	V	C	V	C	V	A
J. L.[1]	42.8	43.6	15.7	14.3	48.0	49.1	9.8	8.1	5.9	6.2	46	68	..	2.7	4.2	129	98	2.8	1.4	107	108	...
A. S.	46.2	45.4	11.9	11.5	49.3	50.0	8.1	7.2	3.8	4.3	74	74	..	2.8	3.2	159	123	2.1	1.7	128	102	...
A. R.[2]	47.0	41.6	17.2	18.1	51.3	52.0	12.9	9.8	4.3	8.3	74	52	..	3.2	4.3	187	128	2.5	2.5	81	62	...
R. T.[3,1]	44.2	42.9	14.8	13.9	49.6	49.4	9.4	8.2	5.4	5.7	33	30	..	1.8	1.7	177	103	5.4	3.4	80	60	...
A. H.[4,1]	36.0	36.0	14.4	13.0	42.5	42.6	8.6	5.3	5.8	7.7	56	36	..	3.2	2.8	203	113	3.6	3.1	129	103	...
O. G.[4,1]	26.2	26.2	12.9	13.4	30.9	33.2	7.7	5.3	5.2	8.1	63	50	..	3.3	4.1	172	121	2.7	2.4	104	88	...
J. H.[4,1]	48.8	50.0	16.7	16.2	55.5	58.7	9.8	6.5	6.9	9.7	64	48	50	4.4	4.7	200	88	3.1	1.8	132	84	120
J. W.[5]	27.2	26.2	11.5	11.0	31.1	29.8	7.2	6.7	4.3	4.3	42	50	52	1.8	2.2	155	113	3.7	2.3	92	72	106
E. W.[4,5,1]	52.4	54.1	9.7	9.9	59.0	59.3	4.5	4.1	5.2	5.8	46	37	44	2.4	2.1	183	117	4.0	3.2	94	80	90
J. A.[6]	47.7	50.8	16.2	17.0	52.1	59.1	11.2	7.8	5.0	9.2	74	50	54	3.7	4.6	160	80	2.2	1.6	80	64	100
Mean	41.9	41.7	14.1	13.8	46.9	48.3	8.9	6.9[7]	5.2	6.9[8]	57	50	50	2.9	3.4	173	108[9]	3.2	2.3[7]	103	82[10]	104

CBF—Cerebral blood flow, cc.100 gm/minute.

$CMRO_2$—Oxygen utilization per 100 gm. brain/minute.

MBP—Mean blood pressure = diastolic plus pulse pressure/3.

CVR—Cerebrovascular resistance = $\frac{MBP}{CBF}$

P.R.—Pulse rate.

C—Control.

V—After veriloid intravenously.

A—After atropine (1 mg.) and veriloid.

[1] Moderate encephalopathy.

[2] Patient hyperventilated after the veriloid.

[3] Patient had cerebrovascular accident six months previously.

[4] Associated congestive heart failure.

[5] Uremia—BUN—J. W. = 40; E. W. = 34.

[6] Severe hypotension with EKG changes.

[7] Statistical significant change from control value ($p = 0.04$).

[8] Statistical significant change from control value ($p = 0.02$).

[9] Statistical significant change from control value ($p < 0.01$).

[10] Statistical significant change from control value ($p = 0.03$).

COMMENTS

Pharmacology. Haultain[12] reported the effectiveness of *Veratrum viride* in the treatment of eclampsia in 1914. This has since been repeatedly substantiated.[13,14] Prior to that time the opinion existed that the drug exerted its hypotensive effect by slowing the heart rate and decreasing cardiac output. However, Cramer,[15] at the request of Haultain, undertook a study of the pharmacodynamics of this drug which have since been elaborated upon but not basically altered. He demonstrated that in experimental animals (cats and rabbits) the pulse rate and blood pressure were reduced by reflexes which arose in the heart and lungs and that these reflexes were mediated via the vagus nerve. When the vagi were cut, *Veratrum viride* had very little effect on the cardiovascular sys-

tem due to interruption of both the afferent part of the reflex arc as well as the vagal efferent outflow. This pharmacologic evidence has presented a paradox; since if *Veratrum viride* produces its major effect by reflex stimulation of the vagal center, atropine should block the vagal effect on the blood pressure as well as on the heart. Atropine blocks the cardiac effect but does not alter the hypotensive effect. This suggests that the vasodilatation and hypotension may be conducted over efferent pathways other than the parasympathetic (vagus). Recent investigations[16] indicate that the drug depresses the blood pressure by both its reflex effect and by direct central effect.

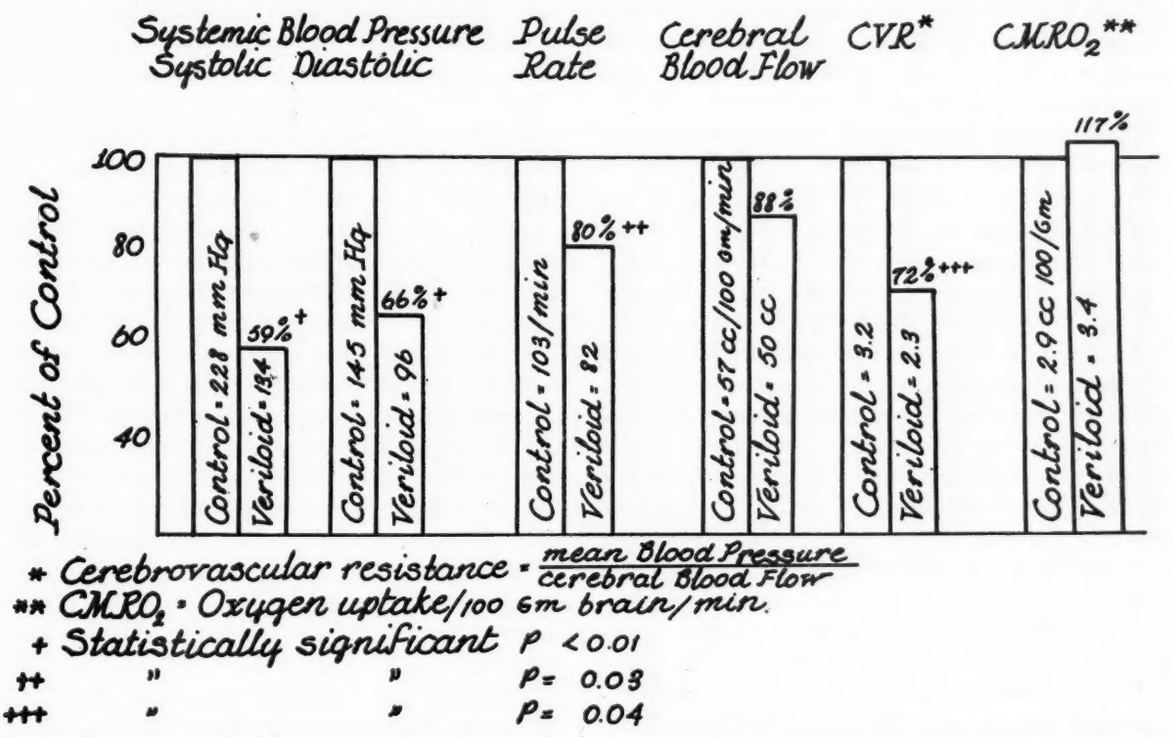

FIG. 2. The mean cerebral hemodynamic and mean blood pressure values for the ten patients are compared to the control studies.

The drug does not act peripherally as an adrenergic blocking agent; since when nor-epinephrine or epinephrine[17] are given, vasoconstriction is just as effective or even more so than without the drug. Likewise, blockade to electrical stimulation of the sympathetic nervous system does not occur. Veratrum depresses respiration[15,18] and produces emesis as part of the reflex pattern. In large doses[15,18] it has a direct depressant effect on the respiratory center.

Recent studies in man have confirmed the earlier animal work. Cardiac output is not depressed.[4,5] In addition, blood flow through the extremities, liver and kidneys is essentially unchanged after stabilization of the blood pressure at lower levels, which indicates generalized vasodilatation. The current study also shows that blood flow through the brain is not altered significantly. Although renal blood flow and glomerular filtration rate are not depressed, there appears to be an unexplained increase in tubular reabsorption of water, thus resulting in oliguria. After sustained hypotension this antidiuretic effect is lost.[4]

Unlike adrenergic blocking (sympathicolytic) agents, vascular hemodynamic reflexes are maintained with veratrum. Response to the cold pressor test remains intact as well as the blood pressure rise after the Valsalva maneuver. Postural hypotension does not occur, and after the drug the systolic pressure decreases proportionally to the diastolic. This can be substantiated from the blood pressure recordings in Tables I and II. Sympathetic vasoconstriction is not inhibited by veriloid[5] and the response to ephedrine and nor-epinephrine remains normal. (Fig. 1A.) Respiratory depression apparently is not as marked in patients as it is in experimental animals. However, it is a distinct possibility as demonstrated in one of our patients (J. H.).

Clinical Comments on Current Study. The ques-

tion of whether or not depression of the blood pressure is desirable in advanced hypertension can be argued pro and con. Although the excretory capacity of damaged kidneys might be further reduced when the blood pressure is lowered, deranged cerebral function secondary to the hypertension is improved by this procedure. This was well demonstrated in the present group of patients who presented predominant evidence of encephalopathy. Therefore, if pathologic cerebral changes or cardiac failure develops secondary to severe hypertension, attempts to reduce the blood pressure are indicated. This is particularly true if renal function is not impaired. In the latter case, renal vascular resistance in the kidney decreases and renal blood flow is not altered.[5] On the other hand, if impairment of renal function dominates the picture, one might well question the indication for reducing the blood pressure to any extent since in this instance one may expect further impairment of renal excretory capacity.[17] An attempt to evaluate alteration of prognosis has not been made in the present study, and admittedly the improved cerebral status may be entirely confined to a symptomatic category.

The administration of veriloid by the intravenous route in comparison to the oral route seems to increase the range between hypotension and nausea and vomiting.[20] Whereas only 22 per cent of the patients exhibited vomiting, all exhibited significant hypotensive responses. The latter was well in excess of the degree that can be obtained following the oral route.[4–7,17,19] The original reports by Wilkins et al.[6] indicated prolonged and encouraging beneficial results using oral veriloid but subsequent investigators have been unable to substantiate these findings.[19] It would appear that the intravenous route is far superior for short-term therapy when immediate and adequate reduction in blood pressure is indicated.

It is of interest that patients exhibiting hypertension secondary to renal disease responded as well as the patients with so-called "essential hypertension." Neither age nor the severity of hypertension affected the response. Since cardiac output is not decreased,[5] the reduction in blood pressure must indicate decreased peripheral resistance due to peripheral vasodilatation. Consequently, the hypothesis that arteriolar hypertrophy with inability of the peripheral vessels to dilate in patients with fixed hypertension is open to question. The present study indicates quite well that the peripheral arterioles can dilate quite adequately in most instances.

Cerebral Hemodynamics. Despite the encephalopathy presented by many of these patients during the control studies, the cerebral blood flow and cerebral metabolism were not abnormal, suggesting that the functional cerebral changes are due to changes in blood pressure dynamics, rather than to alterations in blood flow. The increased arterial pressure may be transmitted to the post-arteriolar vascular bed[21] which in turn increases the capillary blood pressure. This would be reflected in a high capillary filtration pressure and high cerebral tissue pressure, probably increasing the extracellular fluid (edema). There is no evidence available concerning the state of capillary vascular tonus. The only patient exhibiting a cerebral blood flow which was definitely below normal during the control studies (R. T.) suffered a cerebrovascular accident one year previously. That the cerebral vessels were still capable of dilating is indicated by the decrease in cerebrovascular resistance which paralleled the decrease in systemic blood pressure. Thus the cerebral blood flow for the group was not altered significantly ($p = 0.25$) although some of the individual studies did show a reduction. The variability of cerebral blood flow after veriloid indicates fluctuating and unstable cerebrovascular dynamics, since variation of this degree between duplicate cerebral blood flows does not occur when the determinations are done under control conditions. That any decrease in cerebral blood flow was not related to the bradycardia is shown by failure of changes in pulse rate to alter cerebral blood flow when atropine was administered and the pulse rate returned to normal.

The cerebral hemodynamic response to intravenous veriloid is similar to the response to protoveratrine.[22] Since both drugs act in a similar manner, this might be anticipated. These observations plus the observations that drugs which lower blood pressure through activity on other focal points of the autonomic system and yet do not alter cerebral blood flow[23,24] suggest that factors other than the autonomic nervous system are instrumental in regulating cerebral blood flow.

SUMMARY

Twenty-seven patients with severe hypertension, most of whom exhibited various degrees

of encephalopathy, were treated with continuous infusions of intravenous veriloid. The blood pressure decreased significantly in all patients. Seventeen patients were maintained on continuous infusions for prolonged periods of time with improvement of the encephalopathic manifestations in thirteen. However, the drug was discontinued within twenty-four hours in four patients because of vomiting in three and severe hiccoughing in the fourth. One patient died (unrelated to veriloid therapy) eighteen hours after admission. Most of the patients exhibited minor side reactions at some time during the veriloid administration.

The cerebral blood flow studies showed a marked reduction in cerebrovascular resistance which paralleled the reduction in systemic blood pressure, indicating that cerebrovascular dilatation is physiologically possible. Cerebral blood flow was thus maintained. Cerebral oxygen uptake was not altered significantly. These observations are another indication that the regulation of cerebral blood flow is probably not under the control of the autonomic nervous system.

Hypertensive encephalopathy of relatively short duration is not associated with depressed cerebral blood flow. The changes in cerebral function appear to be related to the high arterial pressure which is probably transmitted to the post-arteriolar capillaries resulting in increased cerebral tissue pressure and altered cellular function.

REFERENCES

1. Wood, H. C. A Treatise on Therapeutics Comprising Materia Medica and Toxicology with Especial Reference to the Physiological Action of Drugs to Clinical Medicine. Philadelphia, 1874. J. B. Lippincott & Co.
2. Collins, R. J. The clinical action of veratrum. *Arch. Int. Med.*, 16: 54, 1915.
3. Goodman, L. and Gilman, A. The Pharmacological Basis of Therapeutics. New York, 1940. Macmillan Company.
4. Wilkins, R. W., Freis, E. D. and Stanton, J. R. Essential hypertension. *J. A. M. A.*, 140: 261, 1949.
5. Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H. and Wilkins, R. W. The hemodynamic effects of hypotensive drugs in man. 1. Veratrum viride. *J. Clin. Investigation*, 28: 353, 1949.
6. Wilkins, R. W., Stanton, J. R. and Freis, E. D. Essential hypertension, therapeutic trial of veriloid, a new extract of veratrum viride. *Proc. Soc. Exper. Biol. & Med.*, 72: 302, 1949.
7. Freis, E. D. and Stanton, J. R. A clinical evaluation of veratrum viride in the treatment of essential hypertension. *Am. Heart J.*, 36: 723, 1948.
8. McNair, J. D., Griffith, G. C. and Stephen, E. R. A prolonged study of oral veratrum viride in the treatment of essential hypertension. *Am. Heart J.*, 40: 382, 1950.
9. Borrow, J. G. and Sikes, C. R. The use of purified veratrum viride alkaloids in the treatment of essential hypertension. *Am. Heart J.*, 41: 742, 1951.
10. Stutzman, J. W., Maison, G. L. and Kusserow, G. W. Veriloid, a new hypotensive extract of veratrum viride. *Proc. Soc. Exper. Biol. & Med.*, 71: 725, 1949.
11. Kety, S. S. and Schmidt, C. F. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. *J. Clin. Investigation*, 27: 476, 1948.
12. Haultain, F. W. N. Further experiences with veratrone in the treatment of eclampsia. *Brit. M. J.*, 2: 537, 1914.
13. Irving, E. G. The treatment of eclampsia and pre-eclampsia with veratrum viride and magnesium sulfate. *Am. J. Obst. & Gynec.*, 54: 731, 1947.
14. Bryant, R. D. and Fleming, J. G. Veratrum viride in the treatment of eclampsia. *J. A. M. A.*, 115: 1333, 1940.
15. Cramer, W. On the action of veratrum viride. *J. Pharmacol. & Exper. Therap.*, 7: 63, 1915.
16. Swiss, E. D. and Stutzman, J. W. Site of cardiovascular action of hypotensive veratrum derivatives. *Federation Proc.*, 10: 339, 1951.
17. Mills, L. C., Moyer, J. H. and Miller, S. I. Unpublished data.
18. Pilcher, J. D. and Sollmann, T. Studies on the vasomotor center. XVIII. The effects of veratrum viride and cevadin. *J. Pharmacol. & Exper. Therap.*, 7: 295, 1915.
19. Gropper, A., Surtshin, A. and Hedrick, J. Effects of veriloid on essential hypertension. *Arch. Int. Med.*, 87: 789, 1951.
20. Swiss, E. D. The emetic properties of veratrum derivatives. *J. Pharmacol. & Exper. Therap.*, 104: 76, 1952.
21. Huggins, R. A. Personal communication.
22. Crumpton, C. W., Klingensmith, W. C., Keffer, N. J. and Hafkenschiel, J. H. Effects of protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. *Federation Proc.*, 10: 32, 1951.
23. Hafkenschiel, J. H., Friedland, C. K., Yobaggy, J. and Crumpton, C. W. Effects of 1-hydrazinophthalazine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. *Abstr. Am. Soc. Pharm. & Exper. Therap.*, October 15, 1951.
24. Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H. and Jeffers, W. A. The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. *J. Clin. Investigation*, 19: 408, 1950.

Review

Spatial Vectorcardiography*

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SINCE 1887 when Waller[1a,b] recorded the electromotive changes accompanying the action of the human heart, many advances in the theory and application of electrocardiography have been made. There have been many achievements in the improvement of the technical apparatus employed and in the more accurate interpretation of the records obtained. Unipolar electrocardiography and painstakingly collected autopsy correlations have contributed much to our present knowledge of electrocardiography.

Nevertheless, there is still need for more accurate electrocardiographic diagnosis. Standard technics may fail to reveal evidence of myocardial infarction indicated by clinical evidence and autopsy. As an example of the difficulties encountered, the patterns of conduction delay and bundle branch block patterns are often difficult to distinguish from those of ventricular hypertrophy. Attempts have been made, therefore, to seek additional information by means of exploring electrodes placed in non-standard positions. Thus esophageal, intrabronchial, intracardiac and multiple thoracic leads have been employed but these technics are cumbersome, they are often of limited value and they may not be without danger to the patient. Even with use of these extra leads the desired information may not be obtainable.

The use of such multiple-exploring electrodes is based upon the concept that one can record local potential differences. According to this concept the various anatomic areas of the heart give rise throughout their entire extent to electrocardiographic patterns which are more or less characteristic of the specific area. A further assumption is that these same patterns are reflected onto the overlying areas of the chest wall where they may be recorded without undue interference with each other. An electrode anywhere within the chamber of the left ventricle is thus considered to record a specific and constant pattern which is termed left ventricular cavity potential; similarly, an electrode over the right precordium is thought to reflect right ventricular surface potentials, and so on. The only limiting factor to this type of investigation is the accessibility of the area to exploration by an electrode.

A more recent trend is to minimize the importance of the contributions made by specific "local potentials" to the actual electrocardiograph complex which is recorded since it is believed that none of these "local potentials" retain any identity or lend themselves to present day instrumental analysis. It is considered more advantageous that whatever patterns are recorded represent the total electromotive forces of the heart. In order to secure a more accurate and complete representation of these total forces the technic of spatial vectorcardiography has been developed. It is the purpose of the present communication to discuss some of the theoretic principles, technics and clinical applications of spatial vectorcardiography.

The fundamental theoretic basis of vectorcardiography is the modern dipole theory. In essence, this states that the electrical field which is generated by cardiac activity behaves as though it were produced by a simple battery with positive and negative poles very close together, a battery which is immersed in a homogeneous volume conductor of body tissues and fluids. The positive and negative poles constitute a "dipole" and are actually formed in the body by the relationship of the positively and negatively charged ions of tissue fluid electrolytes. The manner in which the dipole relationship between ions is created and maintained is not relevant to the present discussion which is concerned only with the properties and recording (instrumental analysis) of the dipole itself.

The nature of an electrical field which is

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generated by a single positive and negative pole in close proximity to one another (a dipole) may be considered as follows. A line drawn through the two poles of the dipole constitutes the dipole axis. The direction of this line indicates the direction of positive and negative electricity in the field and hence the direction of the current flow. This line is more familiarly known as the electrical axis of the heart, so named by Einthoven, Fahr and deWaart.[2] The magnitude of the dipole charge or the dipole moment is represented by expanding the length of the dipole axis to a specified standard distance depending upon the voltage generated. The magnitude of the dipole charge is also referred to as "the manifest potential difference in the heart."

If the dipole axis is placed so that it originates at the dipole center, which is the point of zero potential, and if an arrow is placed upon the distal portion so that it is directed toward the positive pole, this single line represents all the properties of the dipole and its field. When these properties are known, namely, the magnitude, direction and sense (positive or negative) of the cardiac dipole, the potential at any point within the electrical field (the body) can be determined.

An addition to the dipole theory was made by Craib and Canfield[3a] in 1927. These investigators showed by both experimental study and mathematical analysis that the cardiac dipole which symbolizes the electrical energy output of the heart at any moment is the resultant of myriads of minute dipoles. These minute dipoles arise during the processes of depolarization and repolarization in minute "muscle elements" throughout the heart. Therefore the cardiac dipole described by Einthoven was actually the resultant of multitudes of minute dipoles originating simultaneously from small muscle elements throughout the heart. Craib attempted to verify this theory by demonstrating that the electrical field generated by a tortoise heart immersed in a saline-filled fish bowl actually did correspond with that which resulted from immersion of an artificial dipole in the same fish bowl.[3a,b] Further experimental verification and clarification has resulted from Craib's study of muscle strips and from the work of many other investigators including Wilson and his co-workers,[4] Burger and VanMilaan,[5a,b,c] and Cronvich and his co-workers.[6]

Relationship between Vectorcardiography and the Dipole Theory. Vectorcardiography is a method for measurement and presentation of the resultant cardiac dipole. The measurement is in terms of vector quantities. A vector quantity is simply a directed quantity, namely, one which has magnitude, direction and sense (positive or negative). This is distinguished from such quantities as mass, volume and potential difference which have no reference to direction. These are referred to as scalar quantities. Since a dipole represents a physical force and has the properties of magnitude, direction and sense, it is a vector quantity. It is therefore subject to the mathematical rules governing vector addition and to vector presentation. The method for its geometric presentation is properly called vectorcardiography.

The mathematical symbol which represents a vector quantity is an arrow. The direction of the arrow indicates the direction of the electromotive force in space, the length of the arrow indicates the magnitude of the force and the head of the arrow points (in the present instance) in the direction of the positive field.

This discussion can be summarized by stating that at every instant of cardiac activity myriads of minute or "elementary" dipoles arise, each of which develops an "elementary" electromotive force which can be represented by a vector. Each "elementary" dipole contributes to the magnitude, direction and sense of the total or resultant electromotive force. Therefore, at any one instant one dipole, which is the resultant of all "elementary" dipoles, and one vector, the resultant of all elementary vectors, can be used to represent the potentials and characteristics of the cardiac electromotive force within the body. This resultant vector is termed the instantaneous cardiac vector.

The sequence of excitation of the ventricular musculature and the generation of electromotive forces which follows the excitation are determined by the anatomy of the bundle of His and the Purkinje fibers. Only general information can be secured as to the order of the spread of excitation by the study of galvanometric deflections from leads at or near the heart since these are merely recording points in the field of the resultant dipole. This was clearly pointed out by Fahr in 1920.[7]

The heart can be considered to be a spherical shell with a septum dividing it into two chambers. The stimulus appears to reach the muscle fibers of the anterior-superior segment of the septum first.[8] The balance of forces at this time is oriented so that the vector of the septal balance

is directed anteriorly and to the right. Thereafter, many segments of the septum and ventricular walls are stimulated simultaneously. At any one time only the net balance or sum of all forces generated at that time is available to instrumental analysis.

The advance of the wave of depolarization creates dipoles across the boundary between the unexcited and excited tissue. The positive pole appears in advance of the negative one. The electromotive forces generated by diverse muscle segments change from instant to instant during the progression of the excitation. The instantaneous vector which is the resultant of all "elementary forces" correspondingly changes from instant to instant throughout the period of excitation, i.e., depolarization and repolarization.

The heart and its active muscle segment have a three-dimensional arrangement. The instantaneous vectors representing the magnitude, direction and sense (polarity) of the electromotive field forces of each moment will correspondingly have a three-dimensional or spatial orientation, i.e., left or right, superior or inferior, anterior or posterior. The terminal points of all instantaneous vectors throughout a cardiac cycle inscribe a spatial cardiac vector loop which also has a three-dimensional character. Spatial vectorcardiography is a technic for the visualization of the spatial character of this vector loop at each moment. All the information as to the field strength of the electromotive forces created through cardiac activity is contained within this spatial cardiac loop.

From the cardiac vector loop one can also deduce certain information concerning the balance of forces contributed by the muscle segments which are active at any one time. Since sufficient information about the normal instantaneous progressive balance of force has been acquired, deviations from these patterns can be ascribed to specific changes of the contributing muscle elements.

The approach to the recording of the electrical phenomena of the heart which has just been outlined is obviously quite different from that which underlies most of the work with so-called "unipolar exploring leads." The basic tenet of this latter concept is that the electromotive forces generated by localized muscle areas are available to instrumental analyses. Certain specific electrocardiographic patterns are therefore thought to represent the potentials of specific anatomic areas of the heart without appreciable interference from those created at a distance. Thus an rS* pattern is thought to be representative of a right ventricular cavity or surface potential because this type of complex is obtained in leads from those locations. A qR pattern is believed characteristic for the left ventricular surface and a QS pattern for the left ventricular cavity for the same reason.

It is difficult to conceive how it could be possible to record individually each of several electrically active centers which are in close proximity to one another and are immersed in one conducting medium. For this reason all leads, including bipolar or unipolar extremity leads, unipolar thoracic, esophageal, intrabronchial and intracardiac leads, are thought to represent the projection of the cardiac vector onto preselected lines of derivation. Thus an "exploring lead" can be regarded as merely tapping the spatial cardiac vector because only the resultant of all individual fields can be recorded.

Numerous attempts have been made to secure an adequate record of the spatial forces. The placement of electrodes, the selection of the appropriate recording device and the preferable spatial representation have been subject to much controversy.

With the construction of the mean manifest axis, Einthoven, Fahr and deWaart[2] gave vectorial presentation to the electromotive field around the heart as projected to the plane of the right arm, left arm and left leg electrodes. The first attempt to reconstruct the instantaneous vector was made by Horatio Williams[9] (1914) who drew perpendicular lines from homonymous peaks of the electrocardiogram and made them intersect in a polar coordinate system. Mann[10] adapted this technic of vectorial reconstruction to a rectangular coordinate system and determined the value of the vertical component geometrically. He was also the first to indicate the possible importance of vectorial analysis of various electrocardiographic abnormalities.[11] Little use was made of this time-consuming technic, however, since each case required careful construction of the three matched or simultaneously recorded electrocardiograms which formed the basis for the

* The relative amplitude of the deflections of the QRS complex is indicated by the use of the lower case (q,r,s) and upper case (Q,R,S). An rS pattern indicates a small positive deflection followed by a relatively larger negative deflection.

analyses. The subsequent construction of a special three-pole galvanometer[12] permitted the instant visualization and recording of the projection of the vector loop onto the frontal plane, as delineated by the right arm, left arm and left leg. At about the same time the cathode ray tube was applied to this purpose by Schellong,[13a,b] Sulzer and Duchosal,[14a,b] Hollmann and Guckes,[15] and Wilson and Johnston.[16] Attempts to record the projections of the vector cardiac loop to more planes than the frontal were made by Schellong,[13a,b] Vasteseger,[17] Duchosal and Sulzer,[18] Conway, Cronvich and Burch,[19] and more recently by Donzelot, Milovanovich and Kaufmann[20] and by Jouve.[21]

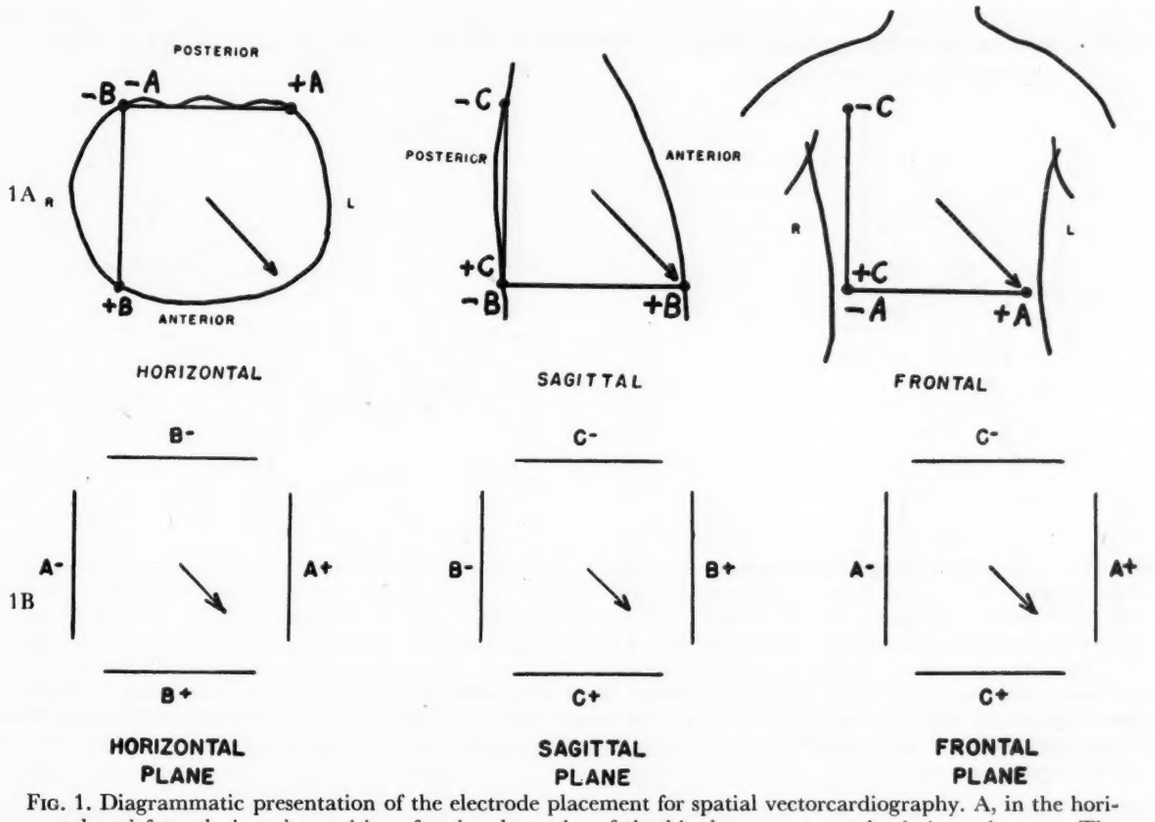

FIG. 1. Diagrammatic presentation of the electrode placement for spatial vectorcardiography. A, in the horizontal and frontal view the positions for the electrodes of the bipolar component lead *A* can be seen. The horizontal and sagittal demonstrate them for the sagittal component lead *B* and the sagittal and frontal plane for the vertical component lead *C*. The three component leads are seen to form three adjoining edges of a cube with their junction at $-A$, $-B$ and $+C$. The arrow indicates the direction a positive charge would take with the polarity selected. B, the component leads are suitably attached to the plates of a cathode ray oscilloscope. The choice of polarity can be seen from the diagram. A positive charge (standardization) would deflect the electron beam of the cathode ray oscilloscope in the direction of the arrow.

TECHNIC

The spatial representation of the electromotive forces differs from investigator to investigator and the details of each cannot be given at this time. It is necessary, however, to evaluate the lead placement of some of the more popular systems employed.

The technic used by Conway and his coworkers[19] is based on the geometric system suggested by Wilson, Johnston and Kossman.[22] In this system the equilateral triangle of Einthoven is considered as representing the frontal plane, and a unipolar electrode located somewhere on the back is considered the summit of an equilateral tetrahedron. The derived placement of the back electrode is such that it records the sagittal component of the electromotive forces.

Since the standard extremity and the unipolar extremity leads are components of the Einthoven triangle, the frontal plane projection of the vector loop as recorded by this technic correlates very well with conventional extremity electrocardiography. However, it is not altogether valid to represent the forces recorded by the extremity bipolar leads in the form of an equilateral

triangle, nor to regard them as determining the frontal plane. The original proponents of the Einthoven triangle regarded it as only an approximation.[2] Burger and VanMilaan[5a,b,c] and Wilson and his associates[23] have shown that the triangle determined by the three extremities is by this technic with patterns recorded by unipolar thoracic and esophageal leads cannot be too satisfactorily accomplished. Similar difficulties were encountered with the sagittal triangular geometric arrangement of electrodes like the one suggested by Arrighi.[25]

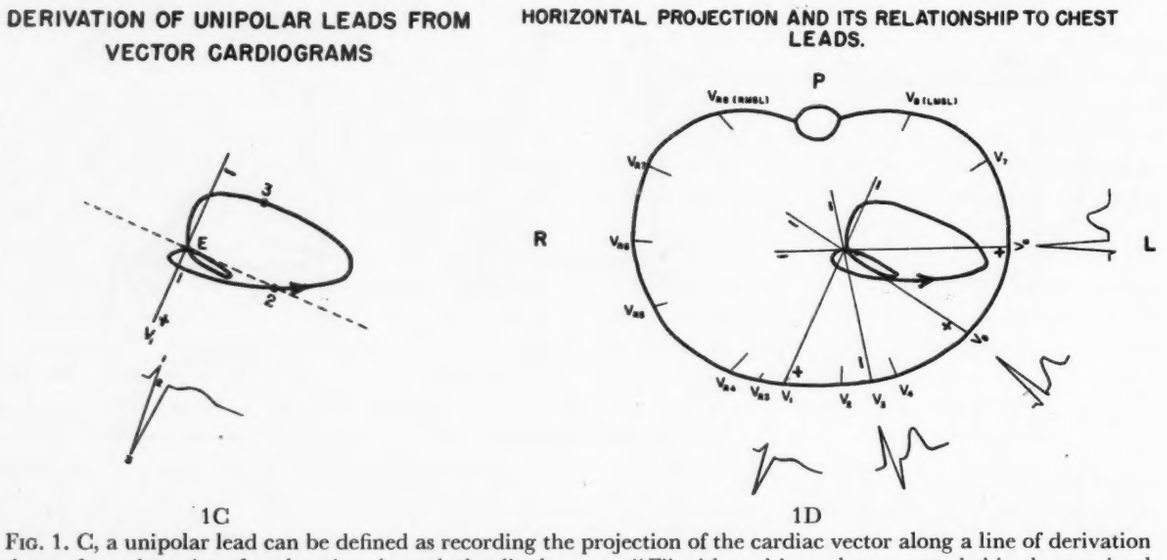

FIG. 1. C, a unipolar lead can be defined as recording the projection of the cardiac vector along a line of derivation drawn from the point of exploration through the dipole center "*E*" with positive voltages recorded in the proximal field and negative voltages in the distal field. Unipolar chest lead V_1 has been chosen in order to make the diagrammatic example less abstract. The dotted line, a vertical upon the line of derivation through the dipole center "*E*," separates the positive field (+) from the negative field (−). The number indicates corresponding points of the vector projection and scalar electrocardiogram. D, diagrammatic presentation of the relationship of unipolar chest leads to the horizontal plane projection of the spatial vectorcardiogram. The approximate position of chest electrodes is indicated. *R*, *L* and *P* refer to the patient's right and left side and posterior aspect.

not equilateral because of the marked discrepancy of the coefficient of the left arm and left leg. Resistance and distance are the main factors responsible for this variability. It is also doubtful that these electrodes represent a plane parallel to the frontal plane.[24] The plane of the three electrodes may deviate by as much as 35 degrees from the true frontal. The effects of such a tilt may be negligible for the frontal plane projection alone but will appreciably alter the record obtained if the plane is used as the foundation for a spatial representation of the electromotive forces of the heart.

Another difficulty in the equilateral tetrahedron system is the location of the summit of the tetrahedron for proper location of the V_B or back electrode. A slight shift in the position of this electrode in any direction may result in complete reversal of the direction of rotation of the vector loop. As a result the polarity is altered. Correlation of the electrocardiograms which are derived from vector loops obtained

Donzelot, Milovanovich and Kaufmann[20] have advocated a lead placement in which VF represents the vertical component, V_2 the sagittal, and V_6 the horizontal. However, since V_2 and V_6 are probably too close to the electrical center of the heart, these components are distorted. In addition, V_2 is at a different horizontal level from V_6 so that the horizontal plane which these leads determine is considerably tilted. Jouve[21] has modified this technic by attempting to place the unipolar electrodes V_2 and V_6 at the level of the electrical center of the heart. However, the former objection, namely that of proximity distortion of the components, still obtains.

Schellong[13a,b] was the first to place the electrodes directly on the thorax and in an orthogonal arrangement. The junction point of the three bipolar component leads was located left anteriorly and superiorly. In order to correct for the proximity of the dipole center to this point Duchosal and Sulzer[18] modified

Schellong's technic and utilized three bipolar leads, their axes forming the adjoining three edges of an orthogonal body or "double cube" with its junction point located at the right posterior axillary line well below the diaphragmatic level. However, by this technic the vertical components had twice the interelectrode distance as compared to the other components. As a result the electromotive forces were unequally represented in the frontal and sagittal plane projections.

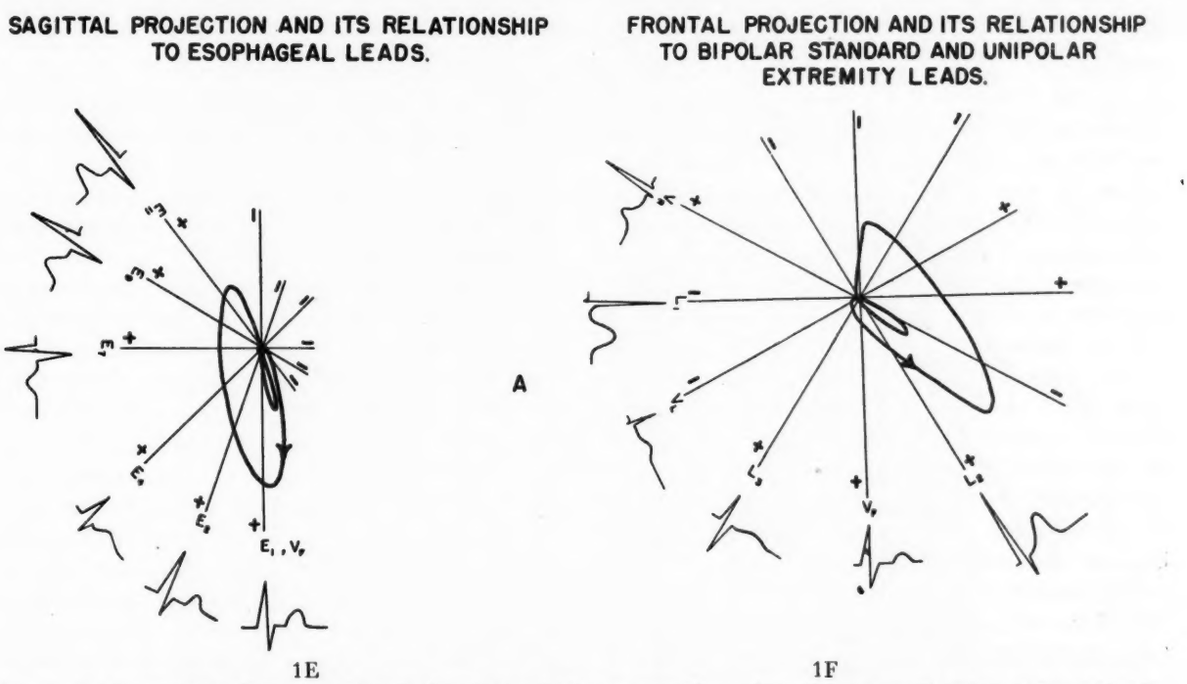

FIG. 1. E, the sagittal plane projection is shown in relation to several esophageal leads. "*A*" refers to the patient's anterior aspect. The lowermost esophageal lead, when placed in the stomach, has the same line of derivation as a unipolar lead V_F. The relationship of specific esophageal leads to the cardiac vector vary somewhat from patient to patient. F, the relationship of the horizontal plane projection to the bipolar and unipolar extremity leads are shown. The triaxial system of Bayley to which are added the lines of derivation of the unipolar extremity leads are superimposed upon the frontal plane projection of the spatial vectorcardiogram.

The technic employed by the present authors utilizes a "cube" form of representation.[24] If one assumes that the electrical center of the heart is at the center of a sphere, a cube can be visualized as enclosed within the sphere in such a manner that the eight corners of the cube represent eight points on the surface of the sphere. The line from the dipole center "E" to adjoining corners would subtend equal internal angles. The electrodes of three bipolar leads are applied to the thorax so as to form three adjoining edges of a cube. Each lead records one of the three components of the total electromotive forces surrounding the heart (A, horizontal; B, sagittal; C, vertical). (Fig. 1A.) Any two of these components determine a plane. Thus the horizontal component, A, and the sagittal component, B, determine the horizontal plane; the vertical component, C, and the horizontal component, A, determine a plane parallel to the frontal plane; and the vertical component, C, and the sagittal component, B, determine the sagittal plane. Suitable amplification and connection to the plates of three oscilloscopes* permit the recording of three projections of the cardiac and vector loops simultaneously. (Fig. 1B.) Equal amplification is made for each of the components. The beam is interrupted each .0025 second (400 cps) to permit time analyses of the records. A photograph is made of the three oscilloscopes so that a complete cardiac cycle is recorded on each negative. A detailed description of the technic and instrumentation and an exact description of electrode placement have been given elsewhere.[24]

The representation of the vectorcardiogram therefore consists of a white center with a rapidly inscribed large loop (QRS sÊ loop) and a much more slowly inscribed smaller loop

* Technicon Cardiograph Machine and Technicon Vectorscope.

(T sÊ loop). The white center corresponds to the isoelectric line of the normal electrocardiogram, i.e., the fixed point at which the cathode ray beam is photographed during the P-R, S-T and T-P intervals. The spread of the wave of accession over the atria is recorded as a small loop (P sÊ loop). The spread of the wave of accession over the ventricles is recorded as the large QRS sÊ loop, with the beam then returning to the center of the screen before the T sÊ loop is inscribed. Each loop is therefore normally recorded as a closed loop. Failure of the beam to return to the center after inscription of the QRS sÊ loop will be recorded as an open loop. This occurs when the S-T vector is not zero but has appreciable magnitude. In the scalar electrocardiogram this is registered as a deviation of the S-T segment.

The direction of inscription of the QRS sÊ loop must be noted in each plane since this permits analysis of the sequence of the spread of the wave of accession, which is of great importance. Automatic instrumental recording of the direction of the vector loop has recently become available.[34] The relative speed with which the deflections are inscribed can be determined by comparing the distance between the interrupted segments of the vector loops. A slow inscription is evidenced by the close proximity of these segments.

From the three projections of the spatial loop recorded in the "cube" technic one can derive the configuration of the routine scalar electrocardiograms, both unipolar and bipolar.[26] The three projections should be considered as different views of the spatial vector loop which represents the total electromotive forces of the heart, as if this loop were viewed through three sides of a transparent cube.

The value of *unipolar leads* lies in their making it possible to record a comparatively true picture of the electromotive forces as they are represented at any one point. Unipolar leads may be considered a means for recording the projection of the total electromotive forces along the line from the electrode through the electrical center, "E," of the heart. This line is referred to as the axis of derivation of the electrode. Whenever the loop is inscribed toward the unipolar electrode, an upward or positive deflection is recorded in the routine or scalar electrocardiogram. Whenever the loop is inscribed away from the unipolar electrode, a downward or negative deflection is obtained. The size of the projection of the loop upon the axis of derivation determines the amplitude of the deflection in the scalar electrocardiogram. (Fig. 1C.) A *bipolar lead* may be considered to record that component of the spatial vector acting in the axis of the lead. The axis of derivation for a bipolar lead is formed by a line joining the two electrodes. The configuration of the standard electrocardiogram so recorded can be derived from the projection of the spatial loop onto the axis of derivation. In a bipolar lead the polarity of each electrode is arbitrarily defined, with the result that designation of a deflection as positive or negative depends upon the polarity chosen.

The electrocardiographic pattern recorded by a unipolar thoracic lead at the level of the dipole center "E" can be predicted from the horizontal plane projection of the vector loop. From the electrode position the axis of derivation is drawn through the center of the loop. The approximate positions of the various electrode placements in relationship to the horizontal projection are indicated in Figure 1D. Although the routine precordial leads are recorded at different levels, there is no significant difference between the derived electrocardiograms and those actually recorded by multiple thoracic leads.

From the sagittal plane projection the pattern of any esophageal lead may be derived. The pattern of VF, which is similar to that recorded by the lowermost esophageal lead E_1 (below the heart), can be derived along the vertical axis as shown in Figure 1E. When the initial deflection in the sagittal plane is upward, a Q wave will be inscribed both in VF and at the lowermost esophageal lead E_1, while a subsequent downward deflection will register an R wave in these leads. The pattern of the esophageal leads at successively higher levels can be similarly determined for both the QRS complex and T wave, according to the method described for unipolar leads.

From the frontal plane the bipolar leads I, II and III and the unipolar extremity leads VR, V_1 and VF can be determined utilizing the Einthoven triangle to which are added the axes of the unipolar extremity leads. The triaxial system of Bayley is a more convenient reference system for deriving scalar electrocardiograms for this purpose. (Fig. 1F.) The projections of the spatial loops upon the three sides of the triangle, or along the intersecting axes of the

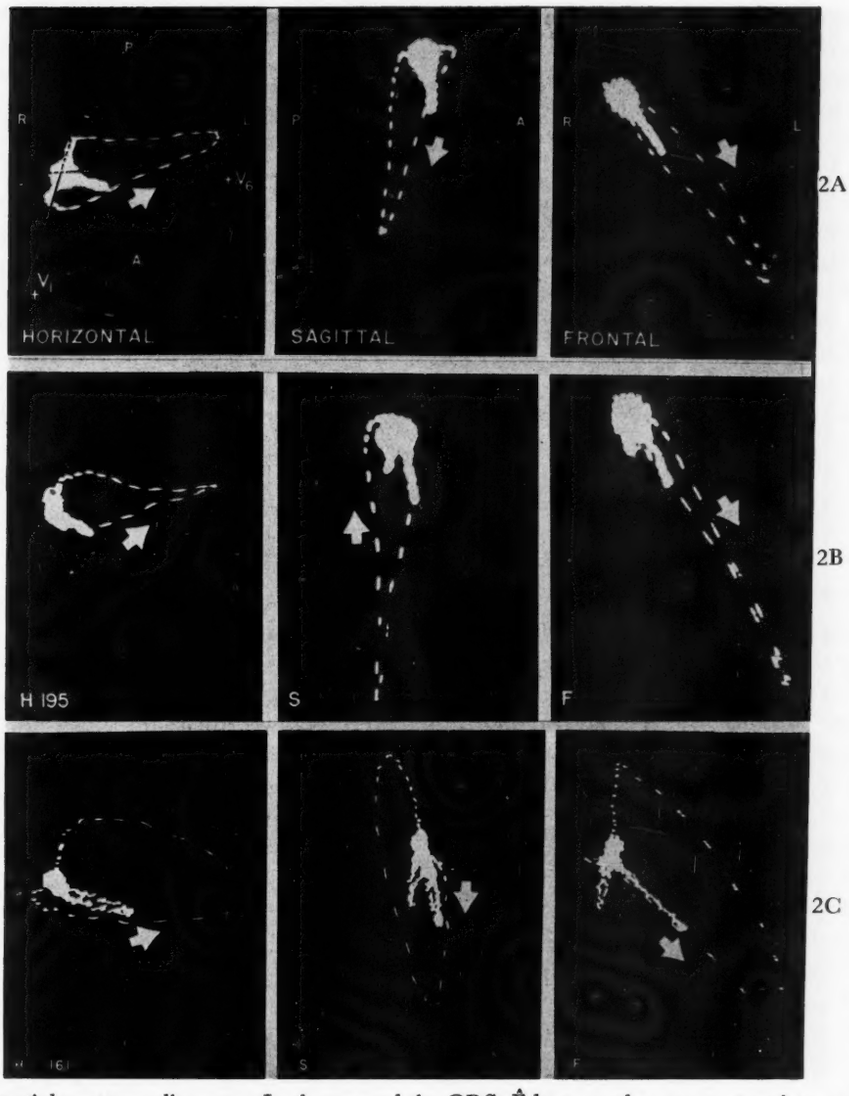

FIG. 2. Normal spatial vectorcardiograms. In the normal the QRS sÊ loop can be seen to start into a right anterior direction, probably representing the vectorial forces created through septal activation. The remainder of the loop develops into a left posterior and inferior direction. The long axis of the smaller T sÊ loop is seen to deviate only slightly from the long axis of the QRS sÊ loop. In normals the direction of rotation of the horizontal projection of the QRS sÊ loop is invariably counterclockwise and in the sagittal plane projection always clockwise. The rotational direction of the QRS sÊ loop in the frontal plane projection varies, moving clockwise in the more vertically placed loops and counterclockwise in the more horizontally placed loops. A, B and C, the three spatial vectorcardiograms, demonstrate well the narrow range obtained in normals. The considerably larger variability of scalar electrocardiograms in normals is due to the varying spatial position of the cardiac vector in relation to the fixed lines of derivation of conventional leads.

Bayley triaxial system and the axes of the unipolar extremity leads, determine the configuration of the scalar electrocardiograms in leads I, II, III, VR, VL and VF.

It has already been pointed out[24] that the plane delineated by the right arm, left arm and left leg often differs from a true frontal plane by as much as 35 degrees. Therefore, differences may occasionally arise between the leads thus recorded and those derived from the frontal plane projection obtained with the "cube" system. These differences are of a quantitative, not qualitative, nature and are not significant.

By inspection of the projections of the spatial vectocardiogram it is possible to predict most of the findings recorded in routine electrocardiograms. If both the T sÊ loop and QRS sÊ loop are similarly oriented, one may predict similar directions for both the T wave and QRS com-

plex in the scalar electrocardiogram regardless of the electrode position. On the other hand, if the T sÊ loop lies on the opposite side of "E" as compared to the QRS sÊ loop, one may state that the T waves will be inverted in those leads in which the QRS complex is upright, and upright in those leads in which the QRS complex is inverted. Gross differences in the speed of inscription of the QRS sÊ loop are readily revealed by the altered proximity of the time markings of the loop. The localization of the delay to specific portions of the loop is useful in the diagnosis of specific impairments in conduction, and therefore in generation, of electromotive forces. If the loop is closed, there is no significant S-T segment deviation whereas an open QRS sÊ loop corresponds to definite deviation.

NORMAL VECTORCARDIOGRAM

Adults. The normal spatial vectorcardiogram is oriented to the left,* inferiorly and somewhat posteriorly.[26] Comparatively little variation is found in regard to the spatial position of the vectorcardiogram in adults. (Fig. 2A and B.) The normal QRS sÊ loop in the horizontal plane projection is characterized by an initial small deflection anteriorly and to the right. The remainder of the loop is then inscribed in a counter-clockwise direction to the left and somewhat posteriorly. The initial deflection to the right inscribes a small R wave in V_1 and a small Q wave in V_6. The large deflection to the left inscribes a prominent S wave in V_1 and a prominent R wave in V_6.

The normal QRS sÊ loop in the sagittal plane projection is characterized by an initial small deflection anteriorly and occasionally superiorly, the remainder of the loop being inscribed downward and somewhat posteriorly in a clockwise direction. High esophageal leads are therefore essentially negative in configuration.

In the frontal plane the normal QRS sÊ loop is inscribed downward and to the left. There may be an initial small deflection to the right and/or superiorly. The more vertical loops in the frontal plane are inscribed in a clockwise direction while the others are inscribed in a counter-clockwise direction.

In the adult the T sÊ loop is usually located anterior, inferior and to the right of the QRS sÊ loop by 10 to 30 degrees. Any marked increase in this angular deviation may prove to be early electrocardiographic evidence of myocardial damage, not readily available from scalar electrocardiograms.

Children. The distinguishing characteristics of the normal routine electrocardiogram in children are mainly attributable to the more anterior orientation of the QRS sÊ loop.[26,27] As in adults, the QRS sÊ loop in the horizontal plane is inscribed in a counter-clockwise direction but the loop is oriented more anteriorly (Fig. 2C) and may extend an appreciable distance to the right. The precordial leads in children are thus characterized by R waves of increased amplitude and S waves of decreased amplitude over the right precordium.

The sagittal plane projection is characterized by an increase in the proportion of the QRS sÊ loop lying anteriorly as compared with the adult. The loop is inscribed in a clockwise direction, as in adults. At times fairly large terminal portions of the QRS sÊ loop are inscribed superiorly and posteriorly.

In normal children most of the frontal plane projections of the QRS sÊ loop are inscribed in a clockwise direction. Terminal portions may be found lying superiorly and to the right so that prominent R waves are found in VR and prominent S waves in lead I.

LEFT VENTRICULAR HYPERTROPHY AND LEFT BUNDLE BRANCH BLOCK

The electrocardiographic distinction between left ventricular hypertrophy and left bundle branch block is at times difficult when only conventional electrocardiograms are available. However, spatial vectorcardiograms display certain characteristics which permit the diagnosis of conduction delay to be made quite readily.[28] When left ventricular hypertrophy is present the QRS sÊ loop in the horizontal projection is characterized by an initial deflection anteriorly and somewhat to the right. (Fig. 3A.) The loop is then inscribed to the left and posteriorly in a counter-clockwise direction. The long axis of the QRS sÊ loop is more posterior than in normal persons, and there is no appreciable alteration in the distances between the time markings. The sagittal plane projection of the QRS sÊ loop is inscribed in a clockwise direction, and the loop is oriented more posteriorly than normally. The QRS sÊ loop in the frontal projection is oriented more to the left than in

* Whenever right or left is used, the reference is to the patient's right or left.

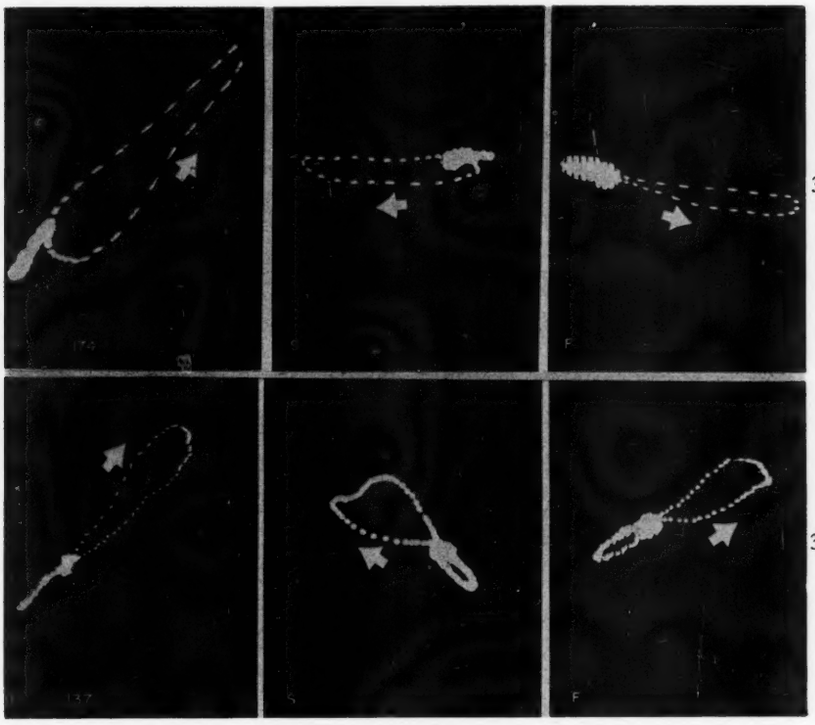

FIG. 3. Left ventricular hypertrophy and left bundle branch block. A, in left ventricular hypertrophy the QRS loop assumes a more horizontal position as can be seen from the sagittal and frontal plane projection. The rotation in the horizontal plane projection is counterclockwise and clockwise in the sagittal plane; this is identical to those encountered in normals. The spacing of the time-markers (400 cycles per second) is also within normal variations. The T loop is in the opposite direction to the QRS loop. B, in left bundle branch block the horizontal plane projection invariably reveals a predominantly clockwise rotation of the QRS loop. In addition, the middle segment of the loop has very close spacing of the time-markings, well demonstrated in all three plane projections. This slowing of the linear velocity is due to the slowed generation of electromotive forces at that point. The T loop is oriented opposite to the QRS loop.

normal persons, and is usually inscribed in a counter-clockwise direction. The T sÊ loop in each projection lies opposite the QRS sÊ loop and there is no evidence of altered proximity of the time markings. The QRS sÊ loop may fail to close prior to the inscription of the T sÊ loop, resulting in an S-T segment deviation in the routine electrocardiogram.

In the presence of left bundle branch block the time markings are much closer together. This increased proximity is usually seen in the middle and late portions of the QRS sÊ loop. (Fig. 3B.) The main portion of the QRS sÊ loop in the horizontal plane projection is inscribed in a clockwise direction, in contradistinction to the rotation found in normal individuals and in those with left ventricular hypertrophy. The QRS sÊ loop is oriented posteriorly, to the left, and often superiorly. In each projection there is increased proximity of the time markings. The T sÊ loop is usually oriented opposite the QRS sÊ loop, and the QRS sÊ loop fails to close prior to the inscription of the T sÊ loop.

In both left ventricular hypertrophy and left bundle branch block the T wave is inverted in the electrocardiogram whenever the ventricular complex is essentially upright since the T and QRS sÊ loops are oppositely oriented in each plane.

RIGHT VENTRICULAR HYPERTROPHY AND RIGHT BUNDLE BRANCH BLOCK

Routine electrocardiography may fail to distinguish right ventricular hypertrophy from right bundle branch block. The precordial lead patterns are at times similar, and rSr′ or rSR′ patterns may be present over the right precordium in both entities. The vectorcardiographic patterns of each are distinctive, however.[29,30] Atypical right bundle branch block

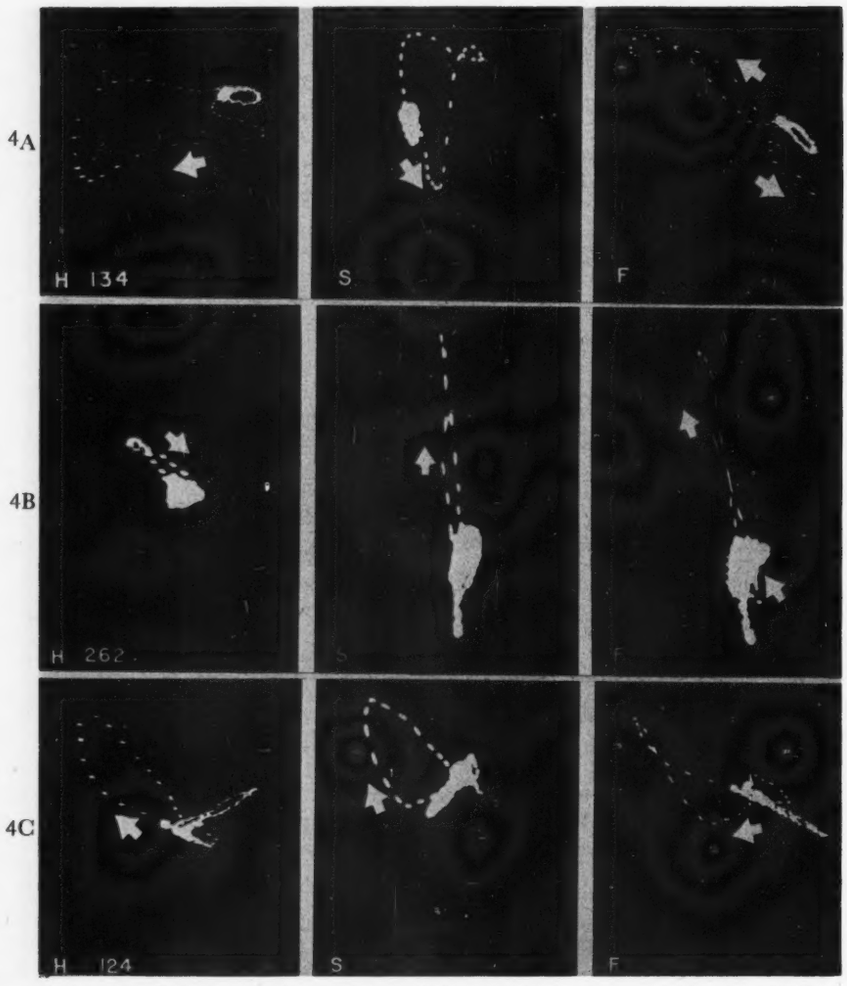

FIG. 4. Right ventricular hypertrophy. A, in moderate right ventricular hypertrophy the QRS loop of the cardiac vector is oriented predominantly to the right (horizontal and frontal plane projection) and somewhat superiorly (sagittal and frontal plane projection). With increasing degrees of right ventricular hypertrophy the T loop assumes a more discordant position in relation to the QRS loop. B, in marked right ventricular hypertrophy the QRS loop assumes a more right (H and F), posterior (H and S) and superior (S and F) position. A further rotation of only slight degree would produce a left axis deviation in bipolar extremity leads. C, in this instance a right ventricular pressure of 200 mm. Hg was recorded due to valvular pulmonary stenosis and interatrial septal defect. The orientation of the QRS loop is posteriorly, superiorly and to the right. This results in small R deep S complexes of scalar unipolar electrocardiograms recorded from the anterior chest wall.

(Wilson type) is characterized by alterations which are usually confined to the terminal portion of the QRS sÊ loop. This terminal portion in each projection is increased in duration, is slow and irregular in contour, and directed to the right and anteriorly. (Fig. 5B.) This terminal portion of the QRS sÊ loop produces the slow, widened S wave of lead I and V_6 and the R′ or late R wave of V_1, and may coexist with any normal or pathologic variety of the QRS sÊ loop.

In right ventricular hypertrophy there is no evidence of a transient slowing of conduction. The QRS sÊ loop is oriented to the right, anteriorly and inferiorly in mild degrees of right ventricular preponderance; (Fig. 4A, B and C) right, anteriorly and superiorly in more severe degrees;[30,31] and right, posteriorly and superiorly in the most marked degrees.[31] When the right ventricular preponderance is mild to moderate, the horizontal projection is characterized by an initial small deflection directed to the right and anteriorly, followed by a large deflection to the left and somewhat posteriorly, then sharply to the right and anteriorly with a clockwise return to the points of origin. (Fig. 5A.) A unipolar electrocardiogram recorded over V_1 will reveal an rSR′ pattern identical

with those encountered in patients with atypical right bundle branch block.[29,32] With increasing degrees of right ventricular hypertrophy, prominent R waves are inscribed over the right precordium and essentially negative ventricular complexes over the left.

MYOCARDIAL INFARCTION

In the normal heart one records the balance of forces generated by the opposing forces of the anterior and posterior walls, the diaphragmatic and superior aspects, and the right and left aspect ef the heart.[26] When infarction of any part of the heart occurs, this area may be considered to be electrophysiologically inert.[33] As a result there is no contribution of this area to the total resultant electromotive forces and there is apparent augmentation of the forces generated by the diametrically opposite area. For example, an infarction localized to the anterior aspect of the heart will augment the forces acting posteriorly, while an infarction of the diaphragmatic aspect of the heart will augment the forces acting superiorly. Since the QRS sÊ loop represents the total resultant electromotive forces of the heart, it will be oriented posteriorly when an anterior infarction occurs and superiorly when a diaphragmatic infarction occurs. (Fig. 6.) Q waves are registered in routine unipolar leads over the site of infarction since the forces are directed away from the infarcted area and therefore away from the electrode. R waves are usually registered opposite the site of infarction since the forces are augmented in the area diametrically opposite the infarcted area. It is not the purpose of this communication to describe the characteristics of the vectorcardiogram for each site of a myocardial infarction; however, it is of value to indicate how a consideration of myocardial infarction on a vector basis can explain some otherwise confusing electrocardiographic patterns.

Since prominent R waves are recorded opposite the site of infarction, the prominent R waves recorded in VR in extensive apical infarction need not be explained by rotational factors but by loss of apical electromotive forces. Prominent R waves in V_1 and V_2 can occur with posterolateral infarctions while diaphragmatic infarctions may be accompanied by prominent R waves in supracardiac esophageal leads.

There may be no evidence of infarction in routine electrocardiograms in some patients but the vector loop may be displaced anteriorly. In such instances infarction of the posterior wall should be suspected.[33]

S-T Segment

Whenever the QRS sÊ loop fails to close prior to the inscription of the T sÊ loop, a deviation of the S-T segment is registered in the electrocardiogram. The direction and degree of this deviation may be determined by drawing a line from the dipole center, "E," of the vectorcardiogram to the onset of the slowly inscribed T sÊ loop. This line represents the S-T vector, with the proximal end at "E" and the distal end as indicated. The orientation of this vector determines in which leads the S-T segment deviates. If this vector is directed to the right and superiorly, the S-T segment will be recorded as elevated in leads VR, V_1 and the high esophageal leads, while the S-T segment will be depressed in leads I, VL, VF, over the left precordium and in the lower esophageal leads. Although the S-T segment deviations in routine electrocardiograms have an essentially similar distribution in left ventricular hypertrophy, left bundle branch block and acute coronary insufficiency, the spatial orientation of the S-T vector differs distinctly in these three conditions.[34]

The T sÊ Loop

The electrical expression of the process of repolarization is given by the T sÊ loop. In certain lower species, such as the frog, the sequence of repolarization is similar to that of depolarization in that the first area depolarized is also the first to be repolarized. The T sÊ loop, which is the result of repolarization, will therefore be oriented along the same axis but will be of opposite polarity as compared to the QRS sÊ loop, which is the result of depolarization. In the warm-blooded species the spatial orientation of the QRS and T sÊ loops will not coincide exactly, with the result that there is a rather narrow range of angular deviation due to an altered time-sequence of repolarization in relation to depolarization. Both processes differ, furthermore, in the speed with which the electromotive forces are generated. The duration of the process of repolarization is not necessarily identical for each muscle area or layer. Localized disturbances of the repolarization process may become evident by an altered contribution toward the T sÊ loop so that its spatial orientation is altered in relation to the long axis of the QRS sÊ loop. Abnormal degrees of angular

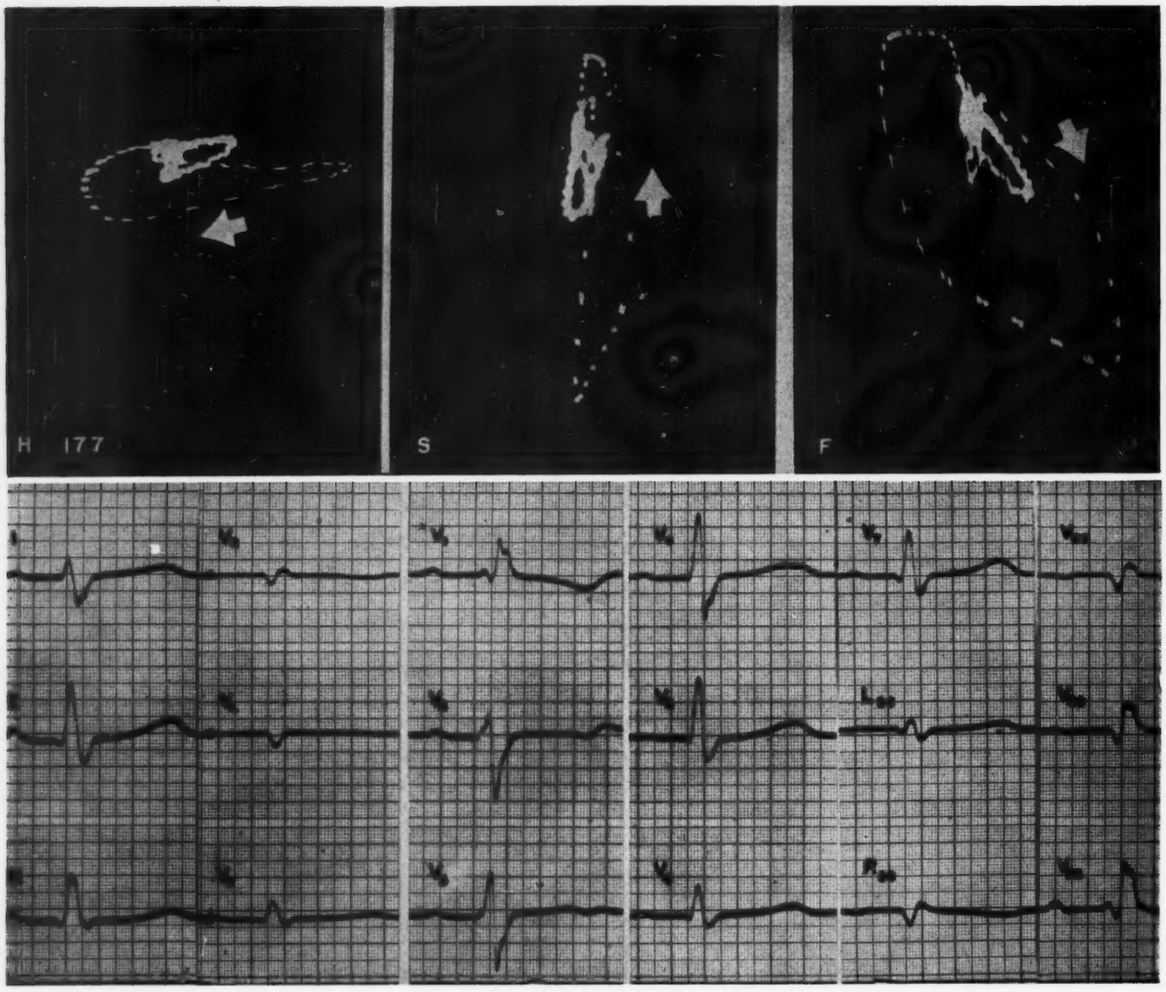

FIG. 5. A, mild right ventricular hypertrophy. The QRS loop of instances of mild right ventricular hypertrophy are oriented to the left and right (H and F) and anteriorly (H and S). No undue slowing of time-markings can be seen. Such a spatial vectorcardiogram results in a set of electrocardiographic leads which can be differentiated from those of atypical right bundle branch block with great difficulty.

deviation of the QRS sÊ to T sÊ loop can be recognized before abnormal T waves are recorded in extremity or chest leads since a relatively large angular deviation is necessary before abnormal T waves are recorded. The yield of diagnostic vectorcardiograms in patients with angina pectoris due to coronary sclerosis is therefore greater than with routine electrocardiograms.[34]

SUMMARY

"The intrinsic effects are those signalling events which occur in the immediate neighborhood of the contacts; the extrinsic effects at some distance from them. In all direct leads from the heart, whatsoever the method employed, these two sets of effects are intermixed and are often very difficult to disentangle. Until complete explanation is possible and until the extrinsic effects are more fully understood than they are at present, we cannot be too circumspect in interpreting curves taken by leads direct from the heart muscle." (Lewis, Meakins, and White, 1914.)[35]

The basic tenet of spatial vectorcardiography which has been stressed is that all electrocardiograms recorded in man—by the very nature of the applicable technics employed—are derivatives of the spatial cardiac vector. When several areas which are generating electricity coexist within one electrolytic conductor, the effective electromotive field force recorded is the balance of all of the forces active at any one time. It is difficult to conceive how a record of electrical forces generated by a certain area can be obtained separately, and how it can be uninflu-

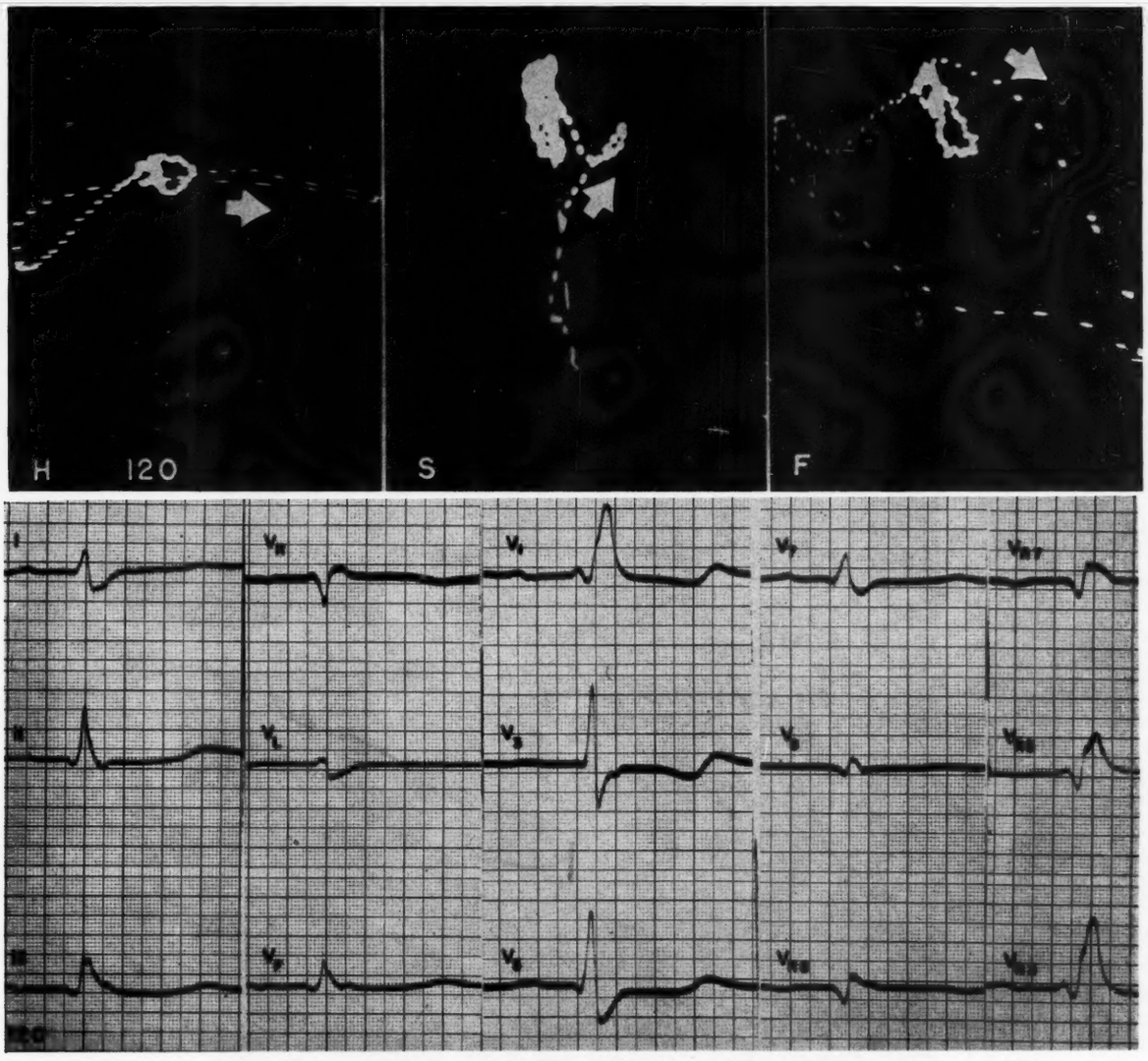

FIG. 5. B, atypical right bundle branch block. A right (H and F) anterior (H and S) "appendix" to QRS loop forms the characteristic change due to right bundle branch block. It shows close proximity of the time-markings which accounts for the long and low voltage S waves in leads I and left-sided chest leads and R waves of similar characteristics in leads V_R and right-sided chest leads. The similarity of the electrocardiogram of atypical right bundle branch block to those of mild right ventricular hypertrophy is striking although the spatial vectorcardiograms are entirely dissimilar.

enced by the electrical forces generated some distance away. The presence of several different areas generating electricity within a conducting medium does not permit such analysis to be made, particularly when semi-direct leads are employed.

It is otherwise difficult to explain the similarity between the records obtained by direct and semi-direct leads when the exploring electrode is moved along a line perpendicular to the cardiac surface. If one assumes that any lead merely "taps" the cardiac vector, an exploring electrode moving along the same axis of derivation will record electrocardiograms of essentially the same configuration since the projections of the cardiac vector are not changed. The voltage would vary according to the distance from the electrode to the dipole center. When the distance becomes very small, as with chest leads, a somewhat disproportionate representation of the positive or negative pole may theoretically occur. It is possible but not probable that this disproportionate representation in the instance of direct leads might provide increased information on "localized" abnormalities.

It is believed that nearly all of the significant information pertaining to the balance of forces throughout the periods of depolarization and

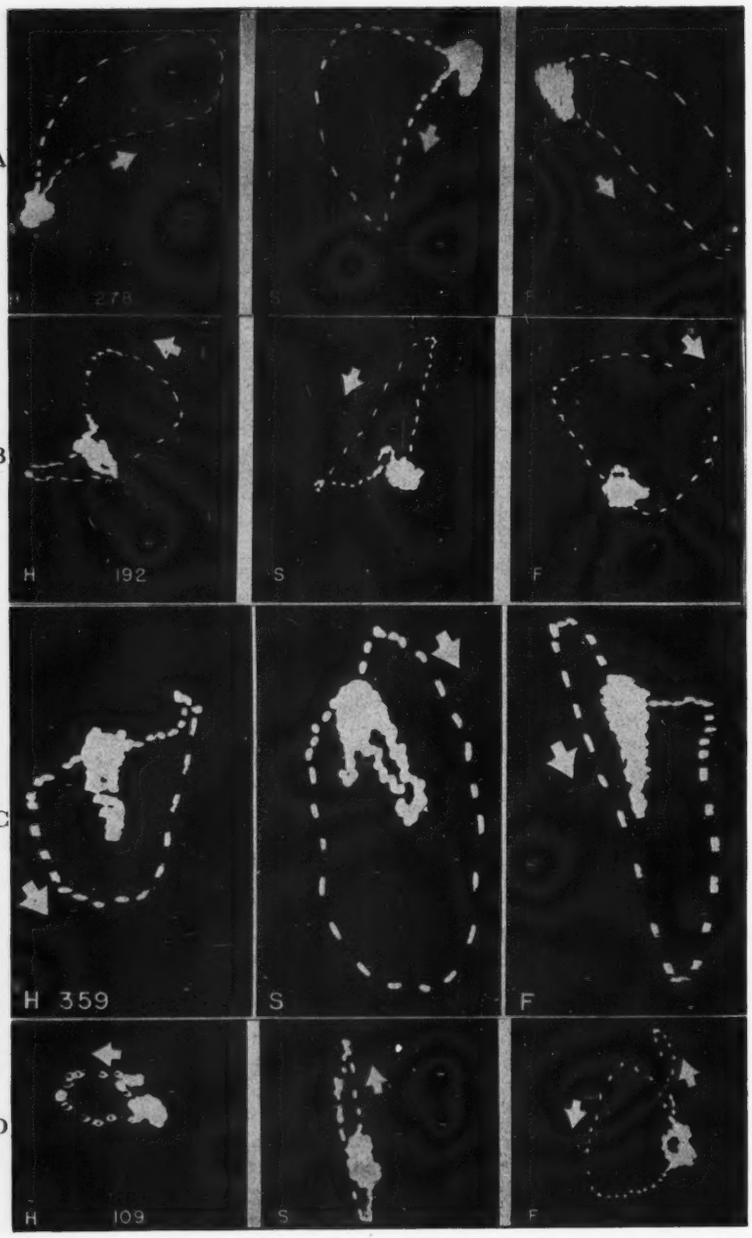

FIG. 6. Myocardial infarction. A, anteroseptal infarction results in the disappearance of the "septal vector," that right anterior initial portion of the QRS loop thought to be due to anterior septal activation. B, in diaphragmatic infarction the electromotive forces generated by the superior aspect of the heart remain unbalanced by those generated by the diaphragmatic aspect. This results in a superior displacement of the QRS loop. C, in posterior and posterolateral infarction the forces generated by the anterior and right anterior aspect become unbalanced, resulting in an anterior or right anterior displacement of the QRS loop. Although such cases may show high R waves in right-sided chest leads, no significant electrocardiographic changes may be seen in others although spatial vectorcardiograms will show characteristic changes of the balance of forces. D, in "apical" infarction, involving the diaphragmatic, anterior and lateral aspect of the left ventricle the QRS loop will be seen to be displaced to the right and superiorly. The right axis deviation seen in such cases is the result of excessive destruction of active left ventricular muscle mass producing a "passive" right ventricular preponderance (while in right ventricular hypertrophy this shift occurs "actively").

repolarization is contained in the cardiac vector. However, it is conceivable that in respect to the recording of the current of injury a decrease in the distance between the exploring electrode and the source of the current of injury might prove advantageous. Until more experience is gained and instrumentation is improved, final judgment should be reserved in this matter. The use of high amplitude recording and continuously moving film should provide supplementary information in connection with this problem.

Although arrhythmias have not been discussed, they can also be recorded and analyzed by similar technics. The use of moving film and high amplitude recording would permit timing and analysis of atrial activity.

While it is possible to derive the configuration of the various electrocardiographic leads from the spatial vectorcardiogram, it is not possible to derive the vector loop from a set of routinely recorded leads. Special leads recorded simultaneously and preferably at increased speed are necessary for this procedure. The error which can arise from even a minute error in phase can be very great, as was pointed out as early as 1920 by Fahr.[7] Since simple vector recording devices are now available, such laborious methods of synthesis would seem to be unnecessary.

Attempts have recently been made to reconstruct the cardiac vector in the horizontal plane from routinely recorded unipolar thoracic leads.[36] A comparison of the loops obtained in this manner with those actually recorded reveals a great many discrepancies. The basic error in attempting to reconstruct the cardiac vector from routine precordial leads derives from the fact that nearly identical unipolar precordial leads may be obtained when the spatial vectors differ markedly and represent distinctly different clinical and physiologic entities.

By the technic of spatial vectorcardiography the total resultant electromotive forces of the heart are recorded. The routine unipolar and bipolar leads can be derived from the appropriate projection of the spatial vectorcardiogram. From the horizontal projection one can derive the configuration of the multiple thoracic leads; from the sagittal projection, the multiple esophageal leads; and from the frontal projection, leads I, II, III, and VR, VL and VF.

By means of spatial vectorcardiography it is possible to distinguish left ventricular hypertrophy from left bundle branch block, and right ventricular hypertrophy from right bundle branch block. Such distinction is not possible at times with routine electrocardiographic leads. Furthermore, infarction of the posterior surface of the heart may be diagnosed by means of spatial vectorcardiography alone.

The technic employed by the authors, which is based on a cube system of electrode placement, was found to represent the spatial position of the cardiac vector most adequately. Although this system does not utilize the principles of the equilateral triangle of Einthoven, the results can readily be linked up with the accumulated information obtained by presently available methods.

The choice and preference of technic depend largely upon what one hopes to obtain from spatial vectorcardiography. If spatial vectorcardiography is to be utilized mainly to explain the electrocardiographic findings in the frontal plane, adherence to a system utilizing the Einthoven triangle might seem desirable. It is believed, however, that the inherent value of spatial vectorcardiography lies beyond this goal. Since all of the electrocardiograms obtained in man are believed to be derivatives of the spatial cardiac vector, the spatial vectorcardiogram should include all of the information which any number and combination of leads can supply. One of the advantages of the cube technic of spatial vectorcardiography lies in the ease of correlating the present routine leads with each plane. The greater yield of clinical information which can be obtained from spatial vectorcardiography as to hypertrophy, conduction disturbance and infarction is another distinct advantage.

REFERENCES

1*a*. Waller, A. D. A demonstration on man of the electromotive changes accompanying the heart's beat. *J. Physiol.*, 8: 229, 1887. (*b*) Idem. On the electromotive changes connected with the beat of the animal heart, and of the human heart in particular. *Phil. Tr. Roy. Soc.*, 180: 169, 1889.

2. Einthoven, W., Fahr, G. and deWaart, A. Ueber die Richtung und die manifeste Groesse der Potentialschwankungen im menschlichen Herzen und ueber den Einfluss der Herzlage auf die Form des Elektrokardiogramms. *Pflüger's Arch. f. d. ges. Physiol.*, 150: 275, 1913.

3*a*. Craib, W. H., with an appendix by Canfield, R. A study of the electrical field surrounding atrial heart muscle. *Heart*, 14: 71–106, 1927. (*b*) Idem. The Electrocardiogram. Great Britain M. Research Council Special Report Series, No. 147, 1930.

4. Wilson, F. N., Macleod, A. G. and Barker, P. S. The Distribution of the Currents of Action and of

Injury Displayed by Heart Muscle and Other Excitable Tissues. Scientific Series No. 10, 1933. University of Michigan Press.

5*a*. BURGER, H. C. and VANMILAAN, J. B. Heart vector and leads, part 1. *Brit. Heart J.*, 8: 157, 1946. (*b*) Idem. Heart vector and leads, part 2. *Brit. Heart J.*, 9: 154, 1947. (*c*) Idem. Heart vector and leads, part 3. *Brit. Heart J.*, 10: 229, 1948.

6. CRONVICH, J. A., CONWAY, J. P. and BURCH, G. E. Standardizing factors in electrocardiography. *Circulation*, 2: 111, 1950.

7. FAHR, G. An analysis of the spread of the excitation wave in the human ventricle. *Arch. Int. Med.*, 25: 146, 1920.

8. LEWIS, T. The Mechanism and Graphic Registration of the Heart Beat, 3rd ed. London, 1925. Shaw & Sons, Ltd.

9. WILLIAMS, H. B. On the cause of the phase difference frequently observed between homonymous peaks of the electrocardiogram. *Am. J. Physiol.*, 35: 292, 1914.

10. MANN, H. A method of analyzing the electrocardiogram. *Arch. Int. Med.*, 25: 283, 1920.

11. MANN, H. Interpretation of bundle branch block by means of the monocardiogram. *Am. Heart J.*, 6: 447, 1930–1931.

12. MANN, H. The monocardiogram. *Am. Heart J.*, 15: 681, 1938.

13*a*. SCHELLONG, F., HELLER, S. and SCHWINGEL, E. Das Vektordiagramm, eine Untersuchungsmethode des Herzens. *Ztschr. f. Kreislaufforsch.*, 29: 497, 596, 1937. (*b*) SCHELLONG, F. Grundzüge einer klinischen Vektordiagraphie des Herzens. Berlin, 1939. Julius Springer.

14*a*. SULZER, R. L'électrogramme a deu dimensions du battement et de la fibrillation ventriculaire du coeur du lapin. *Arch. internat. de physiol.*, 43: 82, 1936. (*b*) SULZER, R. and DUCHOSAL, P. W. Planographie: nouvelle méthode d'enrégistrement électrocardiographique selon deux dérivations simultanies, *Arch. d. mal. du coeur*, 38: 682, 1938.

15. HOLLMANN, W. and GUCKES, E. Das Triogramm und seine klinische Bedeutung. *Arch. f. Kreislaufforsch.*, 4: 69, 1939.

16. WILSON, F. N. and JOHNSTON, F. D. The vectorcardiogram. *Am. Heart J.*, 16: 14, 1938.

17. VASTESEGER, N. N. and ROCHET, J. La stéreovectographie et la stéreovectocardioscopie, méthodes cliniques d'étude de la repartition spatiale des potentiels cardiaques. *Trav. Lab. Inst. Solvay Phys.*, 29: 40, 1944.

18. DUCHOSAL, P. W. and SULZER, R. La vectocardiographie. Basle, 1949. S. Karger.

19. CONWAY, J. P., CRONVICH, J. A. and BURCH, C. E. Observations on the spatial vectorcardiogram in man. *Am. Heart J.*, 38: 537, 1949.

20. DONZELOT, E., MILOVANOVICH, J. B. and KAUFMANN, H. Études Pratiques de Vectographie. Paris, 1950. L'Expansion Scientifigue Francaise.

21. JOUVE, A., BUISSON, P., ALBOUY, A., VELASQUE, P. and BERGIER, G. La Vectocardiographie en Clinique. Paris, 1950. Masson et Cie.

22. WILSON, F. N., JOHNSTON, F. D. and KOSSMANN, C. E. The substitution of a tetrahedron for the Einthoven triangle. *Am. Heart J.*, 33: 594, 1947.

23. WILSON, F. N., BRYANT, M. and JOHNSTON, F. D. On the possibility of constructing an Einthoven triangle for a given subject. *Am. Heart J.*, 37: 493, 1949.

24. GRISHMAN, A., BORUN, E. R. and JAFFE, H. Spatial vectorcardiography: technique for the simultaneous recording of the frontal, sagittal, and horizontal projections. I. *Am. Heart J.*, 41: 483, 1951.

25. ARRIGHI, F. P. El Eje Electrico del Corazon en el Espacio. Tesis de Doctorado en Medicina, Facultad de Ciencias Medicas, Universidad Nacional de Buenos Aires, 1938.

26. SCHERLIS, L., LASSER, R. P. and GRISHMAN, A. Spatial vectorcardiography: the normal vectorcardiogram. VI. *Am. Heart J.*, 42: 235, 1951.

27. LASSER, R. P. and GRISHMAN, A. Spatial vectorcardiography in children: an analysis of high R-waves in right sided chest leads. *J. Pediat.*, 39: 51, 1951.

28. SCHERLIS, L. and GRISHMAN, A. Spatial vectorcardiography: left bundle branch block and left ventricular hypertrophy. II. *Am. Heart J.*, 41: 494, 1951.

29. LASSER, R. P., BORUN, E. R. and GRISHMAN, A. A vectorcardiographic analysis of the RSR′ complex of the unipolar chest lead electrocardiogram. III. *Am. Heart J.*, 41: 667, 1951.

30. LASSER, R. P., BORUN, E. R. and GRISHMAN, A. Spatial vectorcardiography: right ventricular hypertrophy as seen in congenital heart disease. VII. *Am. Heart J.*, 42: 370, 1951.

31. LASSER, R. P. and GRISHMAN, A. Vectorcardiograms obtained in patients with right ventricular hypertrophy whose electrocardiograms display an unusual axis deviation or left axis deviation. IV. *Am. Heart J.*, 41: 901, 1951.

32. LASSER, R. P. and GRISHMAN, A. Spatial vectorcardiography. VIII. Right bundle branch block. *Am. Heart J.*, 42: 513, 1951.

33. SCHERLIS, L. and GRISHMAN, A. Spatial vectorcardiography: myocardial infarction. V. *Am. Heart J.*, 42: 24, 1951.

34. GRISHMAN, A. and SCHERLIS, L. Spatial Vectorcardiography, Philadelphia 1952, W. B. Saunders Company.

35. LEWIS, T., MEAKINS, J. and WHITE, P. D. The excitatory process in the dog's heart. Part I. The auricles. *Phil. Tr. Roy. Soc.*, 205: 375, 1914.

36. GRANT, R. P. and ESTES, E. H. Spatial Vector Electrocardiography; Clinical Electrocardiographic Interpretation. Philadelphia, 1951. The Blakiston Co.

Seminars on Blood Coagulation

Prothrombin and Accessory Factors*

Clinical Significance

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Research in the field of blood coagulation and hemorrhagic diseases has for the past five to ten years been in a dynamic state. The rapidly increasing publications in this field present differences of opinion and conflicting results, an inevitable consequence of the fact that the fundamental problems involved often have not been fully understood. Too often uncritical studies have appeared, with erroneous interpretations of experimental results and occasional misunderstanding of established knowledge. To make for further confusion, a varying terminology is applied to one and the same clotting factor.

The discovery of previously unknown clotting factors and new knowledge concerning the various reacting substances and their interactions now provide a firmer basis for a more complete understanding of the clotting mechanism. By way of general orientation, the specific problem of prothrombin and its accessory factors may be most easily approached by presenting the clotting theory. (Fig. 1.)

Proaccelerin and Accelerin. Proaccelerin is the term first proposed by Astrup (1950) for the clotting factor which I discovered in 1943 and which then was provisionally named the fifth clotting factor or factor V. Until 1943 the so-called classical coagulation doctrine was generally accepted and the problem was rather simple, because we had only to remember that prothrombin is converted to thrombin by the action of thromboplastin and calcium. The first additional factor, proaccelerin, which takes part in the conversion of prothrombin was discovered by study of a case of congenital hemorrhagic disease admitted to the University Hospital of Oslo in the spring of 1943. The prolonged clotting time found in this case was shown to be caused by lack of a previously unknown clotting factor. The deficiency disease was named parahemophilia. The new factor, proaccelerin, was partly purified in a state free from admixture with other coagulation factors, many of its properties were examined and its action in the clotting process analyzed (Owren 1944, 1945, 1946, 1947).

Proaccelerin has the characteristics of a globulin, is thermolabile, is inactivated by trypsin, by acid and alkali at pH below 4 and above 10.5 and also by storage of oxalated plasma. Only small amounts of proaccelerin are removed from plasma by the adsorbents ($Mg(OH)_2$, $Ca_3(PO_4)_2$, $BaSO_4$, $Al(OH)_3$ and Seitz filters) which are used for the removal of prothrombin. This difference in behavior was utilized for the isolation and preparation of proaccelerin free from prothrombin. Addition of concentrated proaccelerin to the plasma of parahemophilia restored the clotting time to normal. Transfusion of normal blood or of concentrated proaccelerin to the patient reduced the clotting time to nearly normal. This effect, however, disappeared in about two days. The survival time of proaccelerin in the circulation, therefore, is only about forty-eight hours at most.

Experiments on parahemophilia plasma as well as on mixtures of partly purified clotting factors showed that proaccelerin acts principally by increasing the velocity of the conversion of prothrombin to thrombin. Proaccelerin itself, however, was shown to be an inactive substance, a precursor or proenzyme which is activated during the clotting process (Owren 1947). It is the active principle, termed accelerin, which governs the velocity of prothrombin activation. Accelerin acts only as a converting factor and is not an integral part of thrombin. Ware and Seegers (1947) first demonstrated

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that the activation of proaccelerin to accelerin is effected by thrombin. Seegers and collaborators (1947, 1948), who have carried out extensive studies on these factors, use the terminology "plasma Ac-globulin" and "serum Ac-globulin." From the data presented it must be concluded that these factors are identical with proaccelerin and accelerin, respectively.

In 1943, the same year that I observed my patient with proaccelerin deficiency, Armand Quick reported findings indicating that prothrombin is a complex composed of two separable factors, prothrombin A and B; prothrombin A being labile and disappearing on storage of oxalated plasma, prothrombin B being stable on storage. Prothrombin B was further found to be adsorbable while prothrombin A could not be adsorbed by the usual adsorbents. Quick later changed the term "prothrombin A" (1943) to "the labile factor" (Quick 1947). The labile factor was not isolated but from the properties mentioned it must be assumed that the labile factor of Quick is identical with proaccelerin and is therefore not a component of prothrombin.

In 1946 Fantl and Nance also reported the presence of an accelerator for prothrombin conversion, demonstrating this in prothrombin-free plasma. The active factor was not isolated but by analyzing their experiments today we can say that the accelerating effect observed was caused by proaccelerin. The co-factor of thromboplastin, described by Honorato (1947), also is identical with proaccelerin.

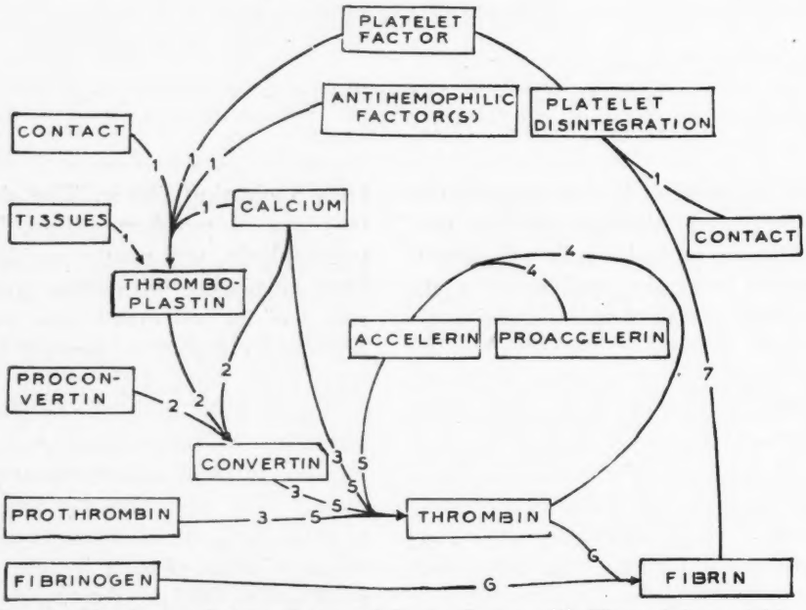


FIG. 1. Blood coagulation: theory of P. A. Owren. (1) Tissue injury yields thromboplastin directly, while contact causes disintegration of platelets and release of a platelet factor, which together with the "anti-hemophilic factor(s)" in the presence of contact and calcium give thromboplastin. (2) Thromboplastin and proconvertin in the presence of calcium forms convertin. An anticonvertin probably exists which opposes the activity of convertin. (3) Convertin together with calcium brings about a minimal conversion of prothrombin to thrombin. (4) This initially formed thrombin starts the accelerator system, i.e., the conversion of proaccelerin to accelerin. An antiaccelerin probably also exists which opposes the activity of accelerin. (5) Accelerin accelerates the conversion of prothrombin to thrombin in the presence of convertin and calcium. (6) Thrombin is now in sufficient quantity to convert fibrinogen to fibrin. (7) Fibrin provokes disintegration of the platelets with further release of the thromboplastic substance already mentioned.

We know a good deal about the properties of proaccelerin and accelerin, especially about their adsorption, precipitation with acid, salts, alcohol or ether, behavior on storage and destruction by heat (Owren 1947, 1948; Seegers et al. 1947, 1948). We have at least one certain method for identification of proaccelerin and accelerin, examination of the specific effect on the clotting disturbance in a proaccelerin-deficient plasma, such as occurs in parahemophilia.

Proconvertin and Convertin. Proconvertin is

another new clotting factor which I first reported in 1947 and which was then provisionally named co-factor V (Owren 1947). Experiments in 1945 to 1947 indicated the existence of a second accessory factor necessary for the conversion of prothrombin to thrombin. It was found that different prothrombin preparations of the same concentration varied greatly in the velocity of thrombin formation even when the conversion conditions with respect to thromboplastin, calcium and proaccelerin (factor V) were quite identical. This varying convertibility was explained by contamination of the prothrombin preparations in varying degree by an unknown converting factor which was adsorbed together with prothrombin. It was not until 1949, however, that we succeeded in fractionating crude prothrombin, prepared from ox plasma, into two components, one being the converting factor, proconvertin, the other being prothrombin itself (Owren and Bjerkelund 1949).

When to prothrombin, prepared free from proconvertin, was added thromboplastin, calcium and proaccelerin or accelerin, no measurable amount of thrombin was formed in the course of thirty to sixty minutes. By adding small amounts of proconvertin, thrombin formation proceeded rapidly, and the velocity of the reaction increased with increasing concentrations of proconvertin up to a certain limit. (Fig. 2.) The presence of proconvertin, therefore, is a prerequisite for thrombin formation under physiologic conditions. Proconvertin, together with thromboplastin and calcium, was also capable of converting prothrombin to thrombin without the presence of proaccelerin or accelerin. The conversion took place very slowly, however, even in the presence of high concentrations of proconvertin This was demonstrated in experiments using isolated factors and also in plasma from the patient with parahemophilia.

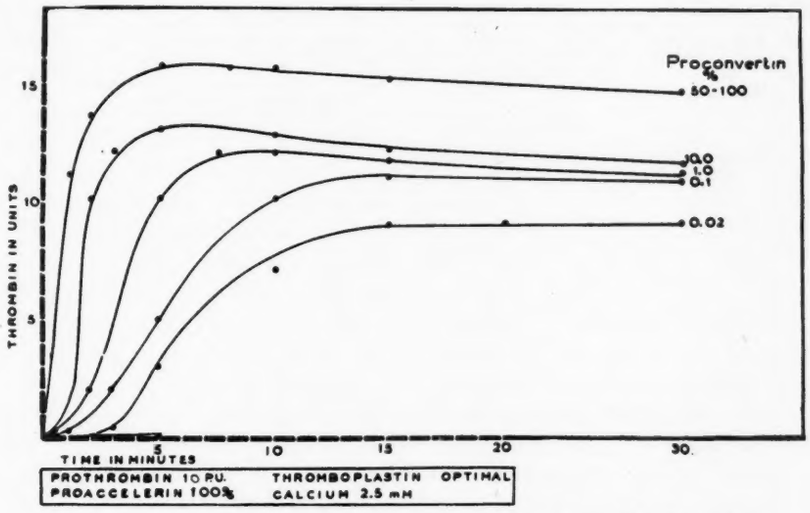


FIG. 2. The effect of proconvertin concentration on thrombin formation.

Proconvertin and thromboplastin do not act directly on prothrombin but first interact in the presence of calcium to produce the prothrombin converting principle which has been named convertin (Owren 1950). The existence of convertin had already been suggested by earlier experiments (Owren 1947). It was then found that during clotting a new principle is formed, provisionally named factor VI, which is the true active principle in the conversion of prothrombin to thrombin. A high activity of factor VI was demonstrated in fresh normal serum which also contains accelerin. Accelerin alone, however, produced by adding thrombin to proaccelerin, did not show any factor VI activity. This finding indicated that serum contains some factor besides accelerin which is necessary to constitute the complete prothrombin converting principle, factor VI. The existence of this additional factor, convertin, was confirmed by experiments on plasma from patients with parahemophilia, in which there is no disturbance caused by the proaccelerin-accelerin system. During incubation of the proaccelerin-free plasma with thromboplastin and calcium, there was a progressive increase in activity of a principle which hastened

thrombin formation upon addition of accelerin and consequently shortened the clotting time. (Owren 1950). (Table 1.) Because the patient's plasma contained no proaccelerin, it was uniquely suitable for following the formation of convertin. In view of the very long clotting

TABLE 1

PARAHEMOPHILIA PLASMA + THROMBOPLASTIN DILUTED 1:50 + Ca

		Clotting Time (sec.)
Without accelerin		120
After addition of accelerin		
Incubation time before addition of accelerin (seconds):	0	28
	15	16
	30	11.4
	45	11.2

time of this plasma it was unnecessary to consider the possibility of any thrombin formation in the short period of incubation, and accelerin could be added at any time to test for the unknown convertin concentration. The interaction of proconvertin and thromboplastin in the formation of convertin was later studied in blood and plasma and also by the use of isolated factors (Owren 1952, Aas 1952). It has been shown that both factors influence the maximal amount of convertin formed.

Convertin is the first and the foremost prothrombin-converting principle produced during normal clotting. Without prior formation of convertin no thrombin will be elaborated under physiologic conditions. For this reason I have chosen the name convertin for this principle and proconvertin for the plasma factor which reacts with thromboplastin in the presence of calcium to form this principle.

The proaccelerin-accelerin system enters as a secondary reaction. Accelerin and calcium cannot convert prothrombin to thrombin in the absence of convertin. Accelerin therefore acts only in the presence of convertin, but in its presence enormously accelerates the reaction. The names proaccelerin and accelerin for the inactive and active form of this factor therefore seem to be adequate.

The existence of a converting factor besides proaccelerin has been suggested by various investigators. During their early work on prothrombin Warner, Brinkhous and Smith (1939) observed a discrepancy between the results obtained by their two-stage method and Quick's one-stage method of prothrombin determination in various species. This observation is explained principally by the large variation in the concentrations of proaccelerin in various species; however, the various concentrations of proconvertin also may play a role.

Many investigators have observed a similar discrepancy between the one-stage and the two-stage method in the determination of prothrombin in dicumarol plasma, the two-stage technic giving higher values. Hurn, Barker and Mann (1947) first called attention to this phenomenon and concluded that dicumarol, besides decreasing prothrombin, also diminishes the conversion of prothrombin to thrombin. Owen and Bollmann (1948) made similar observations in experiments on mixtures of dicumarol plasma and adsorbed plasma and suggested that dicumarol treatment is followed by a decrease in a "prothrombin conversion accelerator." Dam et al. (1948) and Sörbye et al. (1950) obtained irregular dilution curves in mixtures of plasma from vitamin K-deficient and dicumarol-poisoned chicks, also pointing to a decrease, in dicumarol plasma, of an unknown converting factor which they designated the kappa factor.

Dicumarol has little or no effect on proaccelerin (Owren 1948; Olwin 1949). Proconvertin, however, is decreased simultaneously with prothrombin and often to a greater extent (Owren 1950; Koller et al. 1951), a finding which explains the slow conversion of prothrombin to thrombin in dicumarol plasma. There seems to be no doubt, therefore, that the various factors previously found to be decreased simultaneously with prothrombin in dicumarol plasma are all identical with proconvertin.

Mann et al. (1947, 1949, 1951) further demonstrated that preliminary mixing of tissue thromboplastin and calcium with diluted plasma, serum or platelet extracts potentiates the conversion of prothrombin to thrombin, particularly when tested on stored plasma and on plasma of patients receiving dicumarol. The principle increasing the activity of thromboplastin was found to be reduced in dicumarol plasma. It was regarded as part of the thromboplastin complex and was designated "co-thromboplastin activity." It was partly purified by adsorbing serum with tricalcium phosphate and eluting with citrate. The potentiating effect of serum and plasma on tissue thromboplastin is explained by the formation of convertin. The factor found in platelet extract, however, is not proconvertin. It may well be

related to a platelet factor accelerating prothrombin conversion which has also been discussed by Ware et al. (1948).

Alexander and co-workers (1948, 1949, 1950) have made extensive studies on the prothrombin-converting factors present in serum. They demonstrated a prothrombin-converting effect of serum which was not caused by proaccelerin or accelerin and which was termed "the serum prothrombin conversion accelerator" (spca). They believe that spca is evolved from an inactive plasma precursor during clotting. The activity of spca was greatly increased by the addition of thromboplastin. From the various data presented it must be concluded that the effect observed is caused by proconvertin and convertin. Spca prepared from serum usually contains a mixture of proconvertin and convertin, depending on the type of serum used.

Koller in 1951 introduced the term factor VII in place of proconvertin. He uses the same technic as described by Owren and Aas (1951) for the assay of this factor. He found no evidence for the existence of the active principle, convertin, however. A large number of other investigations dealing with the proaccelerin-accelerin system or the proconvertin-convertin system cannot be reviewed here. The clot-accelerating properties of serum were in fact first observed by Bordet and Gengou as early as in 1904.

Prothrombin and Thrombin. For a correct analysis of the process of activation of prothrombin to thrombin, purified preparations of prothrombin, free from admixture with other clotting factors, are needed. The new knowledge concerning proconvertin and proaccelerin has now made this possible. Preparations used previously have usually been more or less contaminated with the converting factors, especially proconvertin, because proconvertin follows prothrombin rather closely in various adsorption and precipitation processes.

The mechanism of activation of prothrombin to thrombin is still a matter of dispute. A major question has been whether prothrombin interacts with one or more of the converting factors in stoichiometric proportions in the formation of thrombin or whether this is a process involving enzymic reactions. Mertz, Seegers and Smith (1939) first presented evidence indicating a quantitative interrelationship between prothrombin and thromboplastin, and Quick (1947) found the same for prothrombin and calcium. Owren (1947) demonstrated that proaccelerin (factor V) disappears during clotting. This finding, however, was explained through the activation of proaccelerin to accelerin (as a part of factor VI), with subsequent inactivation of the accelerin formed. A similar mechanism may explain the quantitative relationship between proconvertin and the amount of thrombin formed because the active principle, convertin, also is slowly inactivated. Previous experiments showing stoichiometric relationships may probably also be explained through interference with these converting factors, which were not known at that time. Further experiments with the use of purified preparations of all the various factors taking part in the reaction are urgently needed to settle this question definitely. Our own investigations support the theory of an enzymic reaction. Chargaff (1948), by high speed centrifugation, has isolated thromboplastin with unchanged activity after it had reacted in the process of prothrombin conversion. Seegers (1949) has demonstrated that a highly purified prothrombin preparation may be slowly activated to thrombin merely by dissolving it in a 25 per cent sodium citrate solution, a finding which indicates that prothrombin contains within itself all the necessary components for thrombin formation.

Preparation of Prothrombin, Proconvertin and Proaccelerin. Prothrombin has usually been prepared from plasma by adsorption (tertiary calcium phosphate, magnesium hydroxide, alumina gel, barium carbonate, barium sulfate) and subsequent elution, by isoelectric precipitation, precipitation with salts or by a combination of these methods. All these preparations are usually contaminated with proconvertin, sometimes also with proaccelerin. The separation of prothrombin and proconvertin was made possible by the finding that proconvertin may be completely removed from ox plasma by passing the plasma once through an asbestos filter pad containing 20 per cent asbestos, while 70 to 80 per cent of the original prothrombin content of the plasma remains in the filtrate (Owren, 1949, 1951). Prothrombin may then be prepared from the proconvertin-free filtrate by adsorption and elution by one of the conventional methods. Ox plasma contains only 30 to 40 per cent of the prothrombin concentration of normal human plasma; the filtered plasma consequently contains about 25 per cent.

The isolation of *proaccelerin* is based on the finding that prothrombin and proconvertin may both be completely adsorbed from oxalated or citrated plasma by filtration through a filter pad containing 40 or 50 per cent asbestos, while proaccelerin is not adsorbed. Instead of asbestos filtration, $BaSO_4$, $Ca_3(PO_4)_2$ and similar adsorbents may also be used. Proaccelerin free from prothrombin and proconvertin is isolated from the adsorbed plasma by fractional precipitation with ammonium sulfate or sodium sulfate, by acid precipitation from diluted plasma (Owren 1947) or by precipitation with ether at low temperature (Owren 1948). For the preparation of proaccelerin, ox plasma is preferable because the concentration of this factor in ox plasma is about 4 times the concentration in human plasma. Proaccelerin prepared from ox plasma is also more stable on storage than proaccelerin of human origin.

Proconvertin is prepared from stored human serum. Normal serum after spontaneous coagulation contains 70 to 90 per cent of the original proconvertin concentration in normal plasma. (Fig. 3.) Unlike convertin and accelerin, the proconvertin in serum is very stable on storage. After storage of serum for eight to ten days at +6°C., proconvertin is the only remaining clotting factor. Some prothrombin may also remain for a rather long time in serum. By adding a small amount of thromboplastin to the blood (2 ml. to 100 ml. of blood) immediately after it is withdrawn, followed by stirring, the prothrombin disappears completely in ten to thirty minutes. Proconvertin is prepared from serum by methods similar to those used for prothrombin preparation.

Methods for the Quantitative Determination of Prothrombin, Proconvertin and Proaccelerin. For a long time there has been a controversy concerning the validity of the principles forming the basis for the one-stage method of Quick and the two-stage method of Warner, Brinkhous and Smith. In Quick's method and in its many modifications, oxalated (or citrated) plasma (or whole blood) is mixed with thromboplastin and calcium and the clotting time determined. This test measures the time needed for the thrombin titer to reach the clotting level in the presence of a fixed amount of thromboplastin and calcium. After the discovery of proconvertin and proaccelerin it became evident that the clotting time ("prothrombin time") as estimated by this method is not a specific measure of prothrombin concentration but varies with the absolute as well as relative concentrations of prothrombin, proconvertin and proaccelerin. One-stage methods using undiluted plasma or blood are insensitive because a significant prolongation of the clotting time does not appear until the concentration of prothrombin, proconvertin or proaccelerin is reduced below 50 per cent of normal. Increased concentrations of one or more of these factors cannot be detected.

TABLE II

Method for Determination of:	Reagents	Clotting Factors Kept Constant in the Reaction Mixture
The combined effect of prothrombin and proconvertin	Adsorbed ox plasma (prepared by passing through asbestos paper filter pads 20% and 50%)	Proaccelerin, Fibrinogen
	Human brain extract	Thromboplastin
	Calcium chloride	Calcium
Prothrombin	Adsorbed ox plasma (asbestos filters 20% and 50%)	Proaccelerin, Fibrinogen
	Stored human serum	Proconvertin
	Human brain extract	Thromboplastin
	Calcium chloride	Calcium
Proconvertin	Proconvertin-free ox plasma (prepared by passing through asbestos paper filter pads 20%)	Prothrombin, Proaccelerin, Fibrinogen
	Human brain extract	Thromboplastin
	Calcium chloride	Calcium
Proaccelerin	Proaccelerin-free human plasma (from parahemophilia or prepared by storage of oxalated plasma)	Prothrombin, Proconvertin, Fibrinogen
	Human brain extract	Thromboplastin
	Calcium chloride	Calcium

In the two-stage technic thromboplastin and calcium are added to dilutions of defibrinated plasma, and the maximum amount of thrombin formed is determined quantitatively by testing the clotting activity on fibrinogen. For obtaining the maximal thrombin titer, and consequently the correct prothrombin value, it is necessary that the conversion of prothrombin to thrombin take place rather rapidly, otherwise some of the thrombin formed will be inactivated by the antithrombin present. When proconvertin or proaccelerin is decreased, therefore, falsely low values may be obtained. It is only with marked depletion of proconvertin or proaccelerin, however, that this slow conversion and reduction in the thrombin yield is of practical importance. When there is a complete lack of proconvertin or proaccelerin no prothrombin, or a minimal amount, will be detected by this method. Such situations occur

very rarely clinically, they are, however, of the greatest importance in experimental studies, especially in relation to the testing of purified prothrombin preparations. (Table II.)

The principle underlying all the following one-stage methods is the use of a clotting mixture in which all factors are kept constant except the one to be determined. The clotting time of such a mixture or reagent will then be dependent entirely upon the amount of the clotting factor lacking, which is added. To obtain great sensitivity the plasma to be tested is diluted usually 1:10 or 1:20. Principles and reagents are illustrated in Table II. The technic has been described in detail elsewhere (Owren 1947, 1949; Owren and Aas 1951), so only a few comments will be made here.

In a method introduced for prothrombin estimation in 1944 a prothrombin-free ox plasma was used as a reagent, in order to obtain a constant and high concentration of proaccelerin in the clotting mixture. Such plasma was prepared by repeated filtration through asbestos filter pads containing 30 per cent asbestos. This filtration also removes proconvertin completely, and the method therefore gives a quantitative expression of the combined effect of reduced prothrombin and proconvertin in the tested plasma. The method has been named the *P* and *P method* (Owren and Aas 1951). It has been used for several years in our department for controlling dicumarol therapy and has proved to be a very reliable and adequate method for this purpose. It is superior to previous methods. It gives a more specific expression of the effect of dicumarol because dicumarol therapy decreases both prothrombin and proconvertin, while proaccelerin is unaltered. The ox plasma reagent is most conveniently prepared by passing the plasma once through an asbestos filter pad containing 20 per cent asbestos, followed by filtration through a filter paper pad containing 50 per cent asbestos.

Addition of a large and constant amount of proconvertin to the reaction mixture used in the P and P method makes possible the specific determination of *prothrombin*. Proconvertin free from prothrombin is obtained from stored normal human serum. After spontaneous clotting of normal blood the serum contains about 70 to 90 per cent of the proconvertin present in the plasma. The prothrombin which often remains in serum is removed by adding a small amount of thromboplastin to the blood, as previously mentioned. The convertin and the accelerin (which is formed during clotting and which remains in serum) are both inactivated by storage. Proconvertin, as already indicated, is the only clotting factor remaining in serum after storage for eight to ten days at +6°C.

For the specific determination of *proconvertin* a clotting mixture is needed in which all factors are kept constant except proconvertin. By passing oxalated or citrated ox plasma through an asbestos filter pad containing 20 per cent asbestos, proconvertin is removed selectively and completely, leaving in the filtrate, besides proaccelerin and fibrinogen, most of the original plasma prothrombin. This procedure therefore provides a reagent for the specific determination of proconvertin. Owing to the relatively low prothrombin concentration in ox plasma, the plasmas to be tested have to be diluted 1:20 in order to eliminate any influence on the clotting time by varying prothrombin concentrations in the tested plasmas.

If one has access to plasma from a patient with congenital lack of proconvertin, this provides an excellent reagent for the quantitative determination of proconvertin. Such plasmas have largely been used for this purpose in our laboratory since 1951.

Proaccelerin is determined by using proaccelerin-free plasma as a reagent. Plasma from parahemophilia is most useful. An artificially proaccelerin deficient plasma is prepared by storing oxalated human plasma. Prothrombin and proconvertin are stable on storage, whereas proaccelerin disappears. The reactivity of the fibrinogen, however, often changes during storage. Stored plasma as a reagent for proaccelerin determination therefore tends to give less reliable results than plasma from parahemophilia.

Prothrombin may also be determined by the two-stage principle. In order always to secure complete conversion of all prothrombin to thrombin, there is added to the conversion mixture, in addition to thromboplastin and calcium, also the active converting factors convertin and accelerin. A reagent containing a high concentration of convertin as well as accelerin, and completely free from prothrombin, is obtained by adding 10 ml. of human brain extract to 100 ml. of normal blood immediately after it is withdrawn, followed by stirring. The prothrombin disappears com-

pletely in ten to twenty minutes. The serum is collected one hour after clotting. It is used in a dilution 1:50. The method is otherwise as described previously (Owren 1947).

TABLE III

Method for Determination of:	Reagents	Clotting Factors Kept Constant in the Reaction Mixture
Convertin	Proconvertin-free plasma	Prothrombin, Fibrinogen
	Adsorbed ox plasma defibrinated by thrombin	Accelerin
	Calcium chloride	Calcium
Accelerin	Proaccelerin-free plasma	Prothrombin, Fibrinogen
	Human serum, stored and then added thromboplastin	Convertin
	Calcium chloride	Calcium
Prothrombin	Adsorbed ox plasma	Fibrinogen
	Adsorbed ox plasma defibrinated by thrombin	Accelerin
	Human serum, stored, and then added thromboplastin	Convertin
	Calcium chloride	Calcium

Methods for the Quantitative Determination of Convertin and Accelerin and a New One-stage Method for the Quantitative Determination of Prothrombin. Based on the final and main reaction in thrombin formation, the conversion of prothrombin to thrombin by convertin and accelerin in the presence of calcium, methods have now been worked out for the specific determination of convertin and accelerin, and also a new method for prothrombin determination. Principles and reagents are illustrated in Table III. For the determination of convertin the clotting mixture used contains an excess of accelerin, and vice versa. It should be stressed that thromboplastin is not used in any of these methods.

A clotting mixture containing constant and high concentrations of prothrombin and accelerin reacts specifically on the amount of convertin added. Similarly, a reagent containing prothrombin and convertin reacts specifically on accelerin, and a reagent containing convertin and accelerin reacts on added prothrombin. The procedure otherwise is similar to the one-stage methods already outlined.

The convertin reagent used is obtained from stored prothrombin-free and accelerin-free serum by activation of the residual proconvertin by adding thromboplastin. The accelerin reagent is prepared by activation of proaccelerin in adsorbed prothrombin-free and proconvertin-free ox plasma by the addition of thrombin. The prothrombin reagent is obtained from proconvertin-free plasma, either human plasma with congenital lack of proconvertin or ox plasma made proconvertin-free by filtration through asbestos filter pads containing 20 per cent asbestos.

From a theoretic point of view these methods have the advantage of being based on a single reaction while other one-stage methods record the total over-all time for different reactions, among others the formation of convertin and the activation of proaccelerin to accelerin, reactions which to a large extent overlap. From a practical point of view they have one drawback; constant reactivity of these systems is difficult to assure since convertin and accelerin are difficult to obtain in stable form.

Clinical Significance of Prothrombin, Proconvertin and Proaccelerin. The main specific purpose of blood clotting is hemostasis, and therefore the most obvious clinical indication of a disturbance of the clotting mechanism is a bleeding tendency. The hemorrhagic diseases have for centuries remained in the realm of medical mystery. During the past two decades, however, sufficient concrete information has been accumulated to make the approach to this problem more effective. The various methods outlined above have proved to be excellent tools for analyzing the various clotting disturbances. A few examples are given.

As illustrated in Figure 3 we may follow the formation of convertin, the active principle produced by the interaction of thromboplastin and proconvertin in the presence of calcium. When the proconvertin concentration is normal, the convertin curve, its rate of formation and maximum of activity will depend only on the thromboplastic activity developed during clotting. By analyzing the convertin formation under standardized conditions, therefore, the various disturbances in the formation of active thromboplastin are disclosed.

The formation of convertin proceeds slowly in thrombocytopenia (Fig. 4) in spite of the fact that the whole blood-clotting time in these cases usually is normal. A deficiency of the platelet substance may be disclosed by the finding of platelets below 50,000. As a consequence of reduced convertin formation only a small amount of proconvertin is utilized and the conversion of prothrombin to thrombin takes place slowly, as illustrated by the reduced consumption or utilization of prothrombin. Similar

findings occur in hemophilia (Fig. 5) caused by a deficiency in a plasma factor which is necessary for the formation of active thromboplastin (the so-called "antihemophilic globulin").

Analysis of accelerin formation represents another method for disclosing clotting disturbances, because the activation of proaccelerin to accelerin depends on the formation of thrombin. A small amount only of thrombin is necessary for the activation of proaccelerin to accelerin. Accelerin formation therefore may be nearly normal in thrombocytopenia but is very slow in hemophilia.

The conversion of prothrombin to thrombin is expressed by the utilization or consumption of prothrombin. The prothrombin consumption curve depends on the combined effect of convertin and accelerin.

Besides being a tool for analyzing various disturbances in the initial reactions in blood clotting, the various methods mentioned are used for analyzing the specific disturbances of prothrombin and its accessory factors.

The most frequent hemorrhagic disease encountered in clinical practice has been ascribed to a deficiency of prothrombin. Prothrombin is synthesized in the liver, and vitamin K is needed for this synthesis. Hypoprothrombinemia may therefore occur in liver diseases and in K avitaminoses. The usual cause of vitamin K deficiency is an inability to adsorb vitamin K, as in obstructive jaundice, biliary fistula, sprue, celiac disease and a few other intestinal diseases. In rare cases K-avitaminosis may occur during treatment with antibiotics because of the sterilization of the

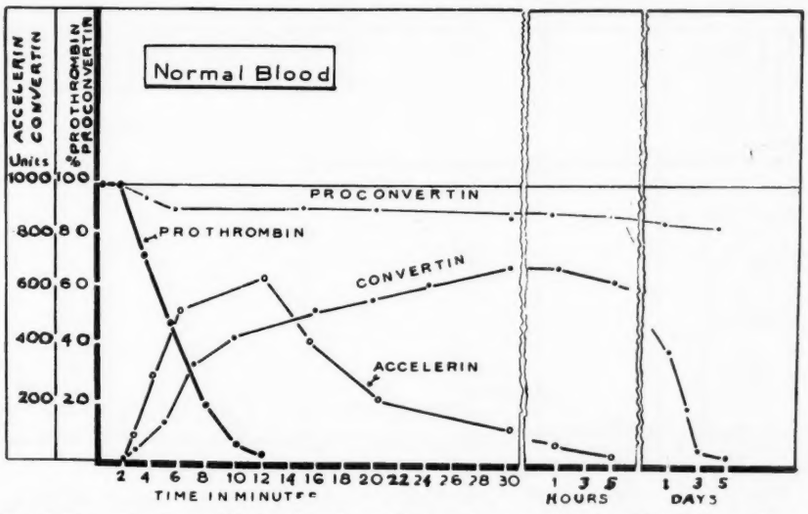


FIG. 3. The "consumption" of prothrombin and proconvertin and the formation of convertin and accelerin during and after clotting of normal blood.

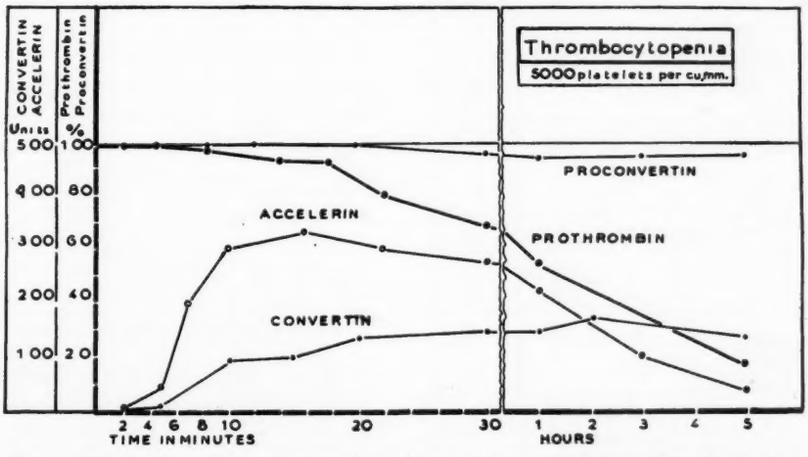


FIG. 4. The "consumption" of prothrombin and proconvertin and the formation of convertin and accelerin during clotting of thrombocytopenic blood.

gut, caused by the fact that a major source of vitamin K is its production by intestinal bacteria. In all these cases of liver disease and K-avitaminoses, however, we have found a decrease of both prothrombin and proconvertin, proconvertin often being depressed to an even greater extent than prothrombin. In vitamin K deficiency administration of vitamin K parenterally is followed by a rapid increase in both prothrombin and proconvertin to a normal level or even higher in the course of twenty-four to forty-eight hours. (Fig. 6.) In hepatic disease vitamin K has little or no effect. (Fig. 7.) These findings indicate that proconvertin, like prothrombin, is synthesized in the liver and that this process needs the presence of vitamin K.

The different response to vitamin K of the hypoprothrombinemia and hypoproconvertinemia in obstructive and parenchymatous jaundice is of clinical importance for the differential diagnosis of jaundiced patients.

Warner, Brinkhous and Smith (1937) first suggested that estimation of the plasma prothrombin level could be used in the assessment of liver function. The specific determination of all three factors has increased the value of this test. A great number of diseases affecting liver function are followed by a decrease in proconvertin and prothrombin; for example, congestive heart failure, thyrotoxicosis, myxedema, anemia and severe acute infections. During

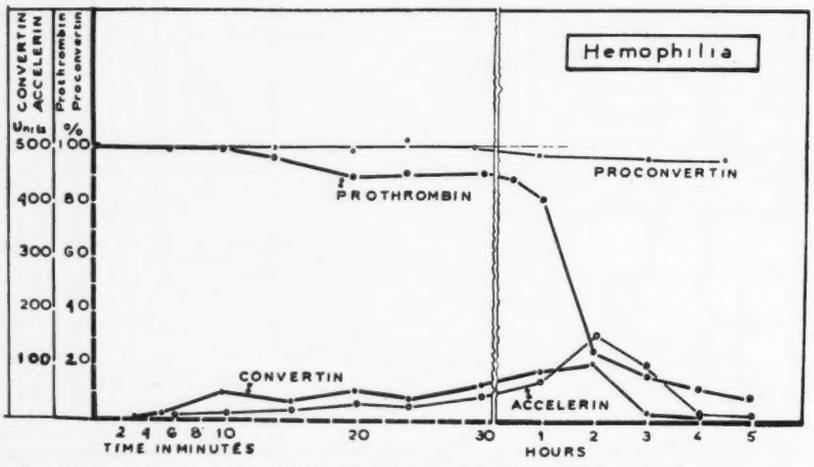


FIG. 5. The "consumption" of prothrombin and proconvertin and the formation of convertin and accelerin in hemophilia.

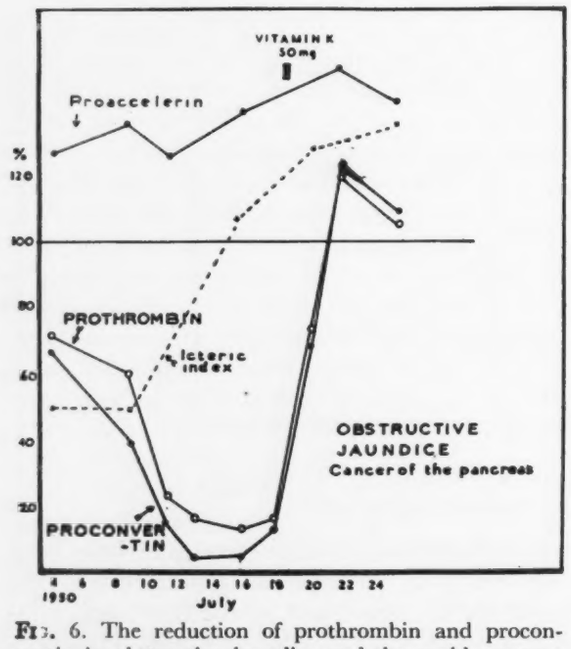


FIG. 6. The reduction of prothrombin and proconvertin in obstructive jaundice and the rapid response to vitamin K.

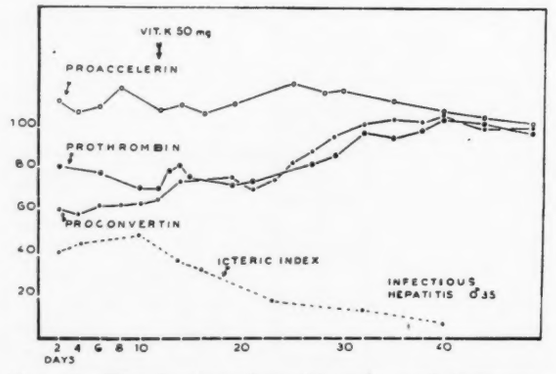


FIG. 7. The hypoprothrombinemia and hypoproconvertinemia in infectious hepatitis do not respond to vitamin K.

recovery the prothrombin and proconvertin levels increase to normal.

In some cases of pernicious anemia and other macrocytic anemias, hypoprothrombinemia (and hypoproconvertinemia) exists. This is not caused by the anemia *per se* but is related to the deficiency of a factor found in liver and brewers' yeast and which differs from vitamin B_{12} and folic acid (Owren 1950). This hypoprothrombinemia is associated with macrocytosis, and both these signs disappear on parenteral administration of the missing factor, which has been termed the protein synthesis factor in pernicious anemia (P.S. factor).

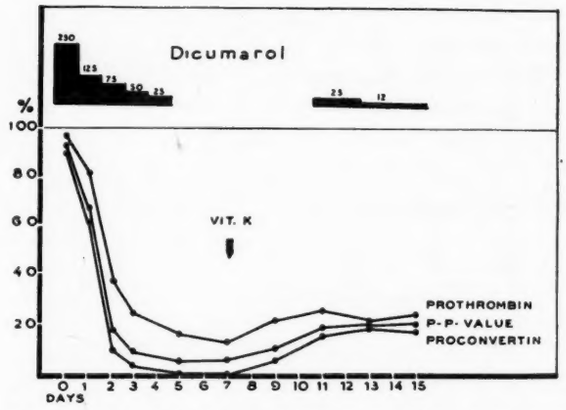


FIG. 8. The effect of dicumarol on prothrombin, proconvertin and the P and P value. Proconvertin is usually decreased to a lower level than prothrombin. It may almost disappear, with hemorrhages while, prothrombin still is in the optimal therapeutic range.

In liver diseases the reduction of proconvertin and prothrombin roughly parallels the degree of damage of the liver parenchyma. With severe hepatic damage the proaccelerin concentration of the blood also decreases. A progressive reduction of all three factors is a serious prognostic sign. When a bleeding tendency occurs in parenchymatous liver disease, it is usually caused by decrease of all three factors. In obstructive jaundice and other diseases associated with K-avitaminosis the bleeding tendency is caused by lowered prothrombin and proconvertin; proaccelerin always being normal, in obstructive jaundice sometimes increased above normal.

The bleeding tendency in dicumarol intoxication is also caused by a deficiency of both prothrombin and proconvertin, proaccelerin always being normal even in severe intoxication. During dicumarol therapy the proconvertin concentration is often depressed to a lower level than prothrombin. Occasionally proconvertin may disappear almost completely while prothrombin is still in the therapeutic range. (Fig. 8.) For adequate control of dicumarol treatment the proconvertin concentration therefore has to be taken into consideration. This can be done by use of the P and P method which in our experience is just as reliable as the specific determination of both prothrombin and proconvertin in guiding dicumarol therapy. (Fig. 9.)

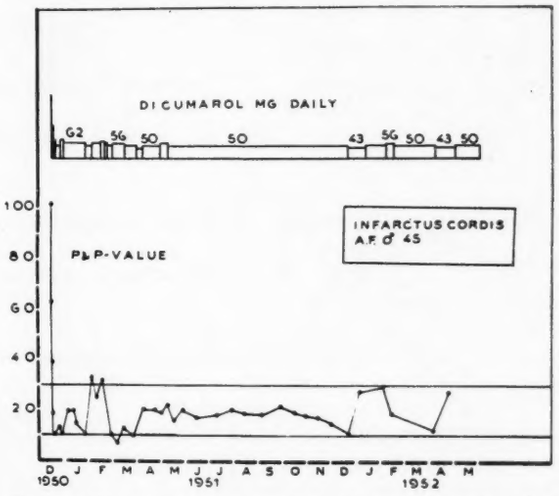


FIG. 9. Dicumarol treatment guided by the P and P method. The optimal therapeutic range for the P and P value has been found to be between 10 and 30 per cent.

Congenital Deficiency of Prothrombin, Proconvertin and Proaccelerin. In 1941 Rhoads and Fitz-Hugh described the first case of "hypoprothrombinemia" which probably was congenital. A few cases have been reported since then. The various reports do not allow any conclusions as to which factor was lacking, prothrombin itself or one of the converting factors, especially proconvertin.

The first case of verified congenital proaccelerin deficiency (parahemophilia) was observed by Owren in 1943. This was a twenty-nine year old female who gave a history of serious hemorrhagic disease since early childhood. Episodes of severe epistaxis and cutaneous hemorrhages had occurred since the age of three years. On one occasion she had had hematuria, since the age of fourteen also menorrhagia severe enough to necessitate blood transfusions. There was no history of hemarthrosis. The clotting time of whole blood was twenty-five minutes; Quick's "prothrombin time" was seventy to eighty seconds and the bleeding time normal.

The patient's plasma showed a complete lack of proaccelerin, also verified by the fact that no accelerin was formed during clotting or upon addition of thrombin.

Congenital proaccelerin deficiency may also occur as a hereditary defect. In 1948 I observed a five year old boy suffering from cutaneous hemorrhages which had occurred intermittently since the age of a few weeks. The clotting time was at the upper limit of normal, Quick's "prothrombin time" was slightly prolonged fifteen to sixteen seconds as compared with a normal thirteen seconds. Proaccelerin was decreased to 35 per cent, while prothrombin (by the two-stage method) and the P and P value (prothrombin and proconvertin combined) was normal. Examination of his mother and brother revealed proaccelerin concentrations of 50 and 45 per cent, respectively, but neither of them had any history of hemorrhagic phenomena. This finding demonstrates that clinical symptoms of a bleeding tendency do not occur until proaccelerin is decreased below about 40 per cent.

In recent years a few more cases of verified proaccelerin deficiency have been reported (Frank, Bilhan and Ekren 1950; Koller et al. 1950; Stohlman, Harrington and Moloney 1951; and Cosgriff and Leifer 1952).

Congenital hypoproconvertinemia was seen by Alexander et al. (1951) and Owren and Aas (1952). Our first case was a thirty-eight year old man admitted to our hospital in September, 1951. He gave a history of abnormal bleeding, especially epistaxis and cutaneous hemorrhages since an early age. There was no history of hemarthrosis except for one occasion at the age of seven years when he had a traumatic hemarthrosis in his right knee. The clotting time in this case varied from normal to slightly above the upper limit of normal. Quick's "prothrombin time" was fifty-five to sixty seconds (normal fourteen seconds). The bleeding time was normal. Specific determination of the clotting factors gave the following results: Prothrombin 95 per cent, proconvertin 3 per cent, proaccelerin 90 per cent and the P and P value 10 per cent. The hypoproconvertinemia showed no response to large doses of synthetic vitamin K. Numerous tests of liver function showed normal values and there were no clinical signs of liver disease.

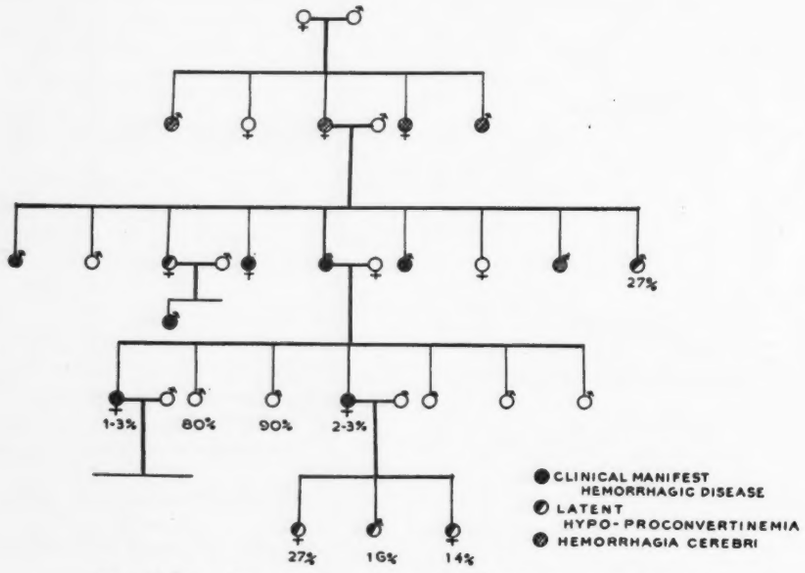


FIG. 10. Family tree of a patient with hypoproconvertinemia.

This year we have observed hypoproconvertinemia also as a congenital and hereditary defect. The first member of the family observed was a forty-six year old female who gave a history of easy bruising and spontaneous epistaxis and repeated hemarthroses particularly in the knee joint since early childhood. She also had menorrhagia, but no abnormal bleedings postpartum. In February, 1952, a spontaneous subarachnoid hemorrhage occurred from which she slowly recovered.

The bleeding time and clotting time were within normal limits. The prothrombin and proaccelerin concentrations were normal but the proconvertin concentration was found to be 2 to

3 per cent, the P and P value 6 to 13 per cent and the Quick's "prothrombin time" fifty-five to sixty seconds. The family history is illustrated in Figure 10. Her three children had no history of hemorrhagic phenomena in spite of proconvertin concentrations of 14, 16 and 27 per cent. Her sister, forty-eight years of age, had suffered from episodes of epistaxis and cutaneous hemorrhages since early childhood. The proconvertin concentration was found to be at the same low level of 1 to 3 per cent. The prothrombin and proaccelerin concentration was normal. None of the five brothers had clinical symptoms of hemorrhagic disease. Only two were examined and showed normal values.

Her father, three of his brothers and one sister had all died of cerebral hemorrhage, some at an age of only about forty years. Four of these siblings had a history of hemorrhagic disease, with easy bruising, epistaxis and prolonged bleeding after dental extraction. Her father also had repeated melena for many years. The paternal grandmother, two brothers and one sister had also died of cerebral hemorrhage, and the same had occurred in a cousin at the age of forty-three. Information is otherwise lacking with respect to other hemorrhagic phenomena in these cases. Her only living uncle, aged sixty-eight, was examined and had a proconvertin concentration of 27 per cent. He had no history of abnormal bleeding.

It follows from the reported findings that the proconvertin concentration has to be reduced to a very low level to give clinical symptoms of hemorrhagic disease. It is further surprising that the whole blood-clotting time in the two cases of severe hypoproconvertinemia was normal or only slightly prolonged. This finding has also been stressed by Alexander.

Based on our experimental results we must conclude that a *complete* lack of proconvertin probably results in uncoagulable blood or a very prolonged clotting time. When a small amount is present, however, sufficient to initiate thrombin formation and consequent activation of proaccelerin to accelerin, prothrombin conversion proceeds at a nearly normal rate because accelerin governs the velocity of this reaction. As illustrated in Figure 11 accelerin formation and prothrombin conversion start a little later than in normal blood but then proceed nearly normally.

The combination of a normal whole blood-clotting time and a prolonged "prothrombin time" of Quick indicates the presence of hypoproconvertinemia. In severe hypoproaccelerinemia both the clotting time and the "prothrombin time" of Quick are prolonged and from experimental results it must be assumed that the same will occur in severe hypoprothrombinemia.

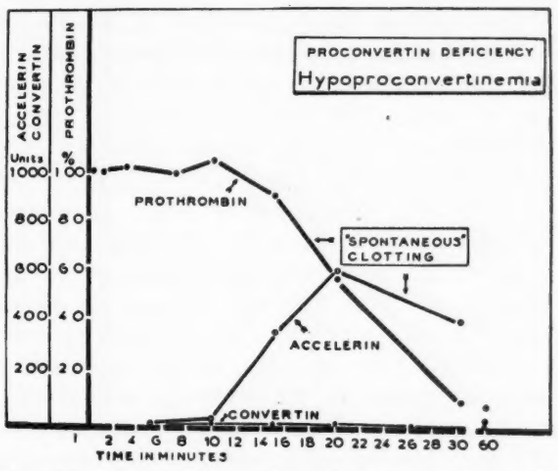


FIG. 11. The initial prothrombin consumption and accelerin formation is slightly delayed in hypoproconvertinemia.

From the point of view of clinical differential diagnosis it has to be remembered that the prolonged clotting time and "prothrombin time" in hypoproacclerinemia are restored to normal by addition of dicumarol plasma and adsorbed plasma, while stored oxalated plasma has no effect. In hypoproconvertinemia and hypoprothrombinemia we have the opposite results, stored plasma being effective while dicumarol plasma and adsorbed plasma are both ineffective. For the differentiation between hypoproconvertinemia and hypoprothrombinemia we may apply the fact that the clotting time and "prothrombin time" in hypoproconvertinemia may be restored to normal by the addition of stored prothrombin-free serum, but not by oxalated ox plasma which has been passed through an asbestos filter pad containing 20 per cent asbestos. The clotting defect in hypoprothrombinemia, on the other hand, is not restored by serum but by the filtered plasma (20 per cent asbestos).

Besides the congenital cases with a specific defect in one of these clotting factors, cases have also been observed with a simultaneous deficiency of two or all three factors. This type of disturbance has also been observed as a hereditary anomaly. In many cases the clotting disturbance is not of sufficient degree to produce

clinical bleeding, except on special occasions such as dental extractions, trauma, operations, and so forth. Such clinical cases of idiopathic "hypoprothrombinemia" have been described by various investigators (Plum 1943, Quick 1947, Giordano 1943, Hagen and Watson 1948 and others).

The various examples given in this short review illustrate how the problem of prothrombin and its accessory factors has implications for a variety of clinical conditions. Many problems which may be related to these factors and their function have not been discussed, however. The significance of reduction of these factors, especially in liver diseases and the hemorrhagic diseases which follow severe depletion of these clotting factors, represents only one aspect of the clotting problem from the clinical point of view. Today we are even more interested in the question of increased coagulability and its relation to thromboembolic disease, a problem of enormous physiologic and clinical importance. In this field important progress has also been made but many problems still remain enigmatic. The mechanisms governing and regulating the fluidity of the blood are no doubt intricate, and important links are still missing. Hypercoagulability has often been demonstrated in association with thromboembolic disease. In our experience this increased coagulability is not caused by increased concentrations of prothrombin, proconvertin or proaccelerin, but seems to be related to the formation of active thromboplastin. At the moment we have no reliable method however, for analyzing the intrinsic potential property of the circulating blood to form active thromboplastin. The new method for analyzing convertin activity and new knowledge concerning the interaction of thromboplastin and proconvertin in the formation of convertin may be of importance also for a more effective approach to this problem.

REFERENCES

Aas, K. Prokonvertin og konvertin. Thesis. Oslo, 1952.

Alexander, B., de Vries, A. and Goldstein, R. *J. Clin. Investigation*, 27: 523, 1948.

Alexander, B., de Vries, A., Goldstein, R. *Blood*, 4: 739, 1949.

Alexander, B. and de Vries, A. *Blood*, 4: 747, 1949.

Alexander, B., Goldstein, R. and Landwehr, G. *J. Clin. Investigation*, 29: 881, 1950.

Alexander, B., Goldstein, R., Landwehr, G. and Cook, C. D. *J. Clin. Investigation*, 30: 596, 1951.

Astrup, T. Advances in Enzymology, vol. 10. Edited by F. F. Nord. New York, 1950. Interscience Publishers, Inc.

Chargaff, E. *J. Biol. Chem.*, 173: 253, 1948.

Cosgriff, S. W. and Leifer, E. *J. A. M. A.*, 148: 158, 1948.

Dam, H. and Söndergaard, E. *Biochim. et biophys. acta*, 2: 509, 1948.

Fantl, P. and Nance, M. *Nature, London*, 158: 708, 1946.

Frank, E., Bilhan, N. and Ekren, H. *Acta haemat.*, 3: 70, 1950.

Giordano, A. S. *Am. J. Clin. Path.*, 13: 285, 1943.

Hagen, P. S. and Watson, C. J. *J. Lab. & Clin. Med.*, 33: 542, 1948.

Honorato, R. *Am. J. Physiol.*, 150: 381, 1947.

Hurn, M., Barker, N. W. and Mann, F. D. *Am. J. Clin. Path.*, 17: 712, 1947.

Koller, F., Gasser, C., Krüsi, G. and De Muralt, G. *Acta haemat.*, 4: 33, 1950.

Koller, F., Locliger, A. and Duckert, F. *Acta haemat.*, 6: 1, 1951.

Mann, F. D., Hurn, M. and Magath, T. B. *Proc. Soc. Exper. Biol. & Med.*, 66: 33, 1947.

Mann, F. D. *Am. J. Clin. Path.*, 19, 861, 1949.

Mann, F. D. and Hurn, M. *Am. J. Physiol.*, 164: 105, 1951.

Mann, F. D., Barker, N. W. and Hurn, M. *Blood*, 6: 838, 1951.

Mertz, E. T., Seegers, W. H. and Smith, H. P. *Proc. Soc. Exper. Biol. & Med.*, 42: 604, 1938.

Olwin, J. H. *J. Lab. & Clin. Med.*, 34: 806, 1949.

Owen, C. A. and Bollmann, J. L. *Proc. Soc. Exper. Biol. & Med.*, 67: 231, 1948.

Owren, P. A. Det Norske Videnskaps-akademi i Oslo, p. 21. Arbok, 1944.

Owren, P. A. *Nord. med.*, 28: 2630, 1945.

Owren, P. A. Proc. Scand. Congr. intern. Med. Gothenburg, June 28, 1946.

Owren, P. A. *Acta med. scandinav., suppl.* p. 194, 1947.

Owren, P. A. *Bull. Acad. Suisse d. sc. med.*, 3: 163, 1947.

Owren, P. A. *Biochem. J.*, 43: 136, 1948.

Owren, P. A. Report of Annual Meeting and Proceedings of The Royal College of Physicians and Surgeons of Canada, p. 107, 1948.

Owren, P. A. *Scandinav. J. Clin. & Lab. Invest.*, 1: 81, 1949.

Owren, P. A. *Scandinav. J. Clin. & Lab. Invest.*, 1: 131, 1949.

Owren, P. A. and Bjerkelund, C. *Scandinav. J. Clin. & Lab. Invest.*, 1: 162, 1949.

Owren, P. A. *Scandinav. J. Clin. & Lab. Invest.*, 2: 241, 1950.

Owren, P. A. Proc. of the third internat. congress of The International Society of Hematology at Cambridge, England, 1950, pp. 22, 379–390, 475. New York, 1951. Grune & Stratton.

Owren, P. A. *Scandinav. J. Clin. & Lab. Invest.*, 3: 168, 1951.

Owren, P. A. and Aas, K. *Scandinav. J. Clin. & Lab. Invest.*, 3: 201, 1951.

Owren, P. A. *Rev. d'hémat.*, 7: 147, 1952.

Owren, P. A. Tr. 5th Conf. on Blood Clotting and Allied Problems. Josiah Macy Jr. Foundation 1952. (In press.)

Owren, P. A. Nye Medisinske Fremskritt, II, H. Achehoug og Co. Oslo, 1952.

PLUM, P. *Acta med. Scandinav.*, 113: 262, 1943.
QUICK, A. J. *J. Biol. Chem.*, 109, 73, 1935.
QUICK, A. J. *Am. J. Physiol.*, 140: 212, 1943.
QUICK, A. J. *Lancet*, 379, 1947.
QUICK, A. J. *Am. J. Physiol.*, 148: 211, 1947.
SEEGERS, W. H. *Proc. Soc. Exper. Biol. & Med.*, 72: 677, 1949.
STOHLMAN, F., JR., HARRINGTON, W. J. and MOLONEY, W. C. *J. Lab. & Clin. Med.*, 38: 842, 1951.
SÖRBYE, Ö., KRUSE, I. and DAM, H. *Acta chem. scandinav.*, 4: 549, 1950.
WARE, A. G., GUEST, M. M. and SEEGERS, W. H. *J. Biol. Chem.*, 169: 231, 1947.
WARE, A. G., MURPHY, R. C. and SEEGERS, W. H. *Science*, 106: 618, 1947.
WARE, A. G. and SEEGERS, W. H. *J. Biol. Chem.*, 172: 699, 1948.
WARE, A. G. and SEEGERS, W. H. *Am. J. Physiol.*, 152: 567, 1948.
WARNER, E. D., BRINKHOUS, K. M. and SMITH, H. P. *Proc. Soc. Exper. Biol. & Med.*, 40: 197, 1939.

Combined Staff Clinic

Mitral Stenosis

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. KENNETH B. TURNER: The allocation of an entire clinic to a single valve of the heart is justified by recent advances in surgical technic which now permit a direct attack upon a stenotic lesion of the mitral valve. It is proper to begin with a consideration of the anatomy and mechanical functioning of that valve. For this, we turn not to the textbooks of anatomy and physiology but to a practicing surgeon, Dr. Elliott Hurwitt, Chief of the Surgical Division at Montefiore Hospital and Clinical Professor of Surgery in Columbia, who has generously given us this opportunity to view an extraordinarily interesting motion picture prepared in the laboratory for surgical research at the Montefiore Hospital by Dr. Adrian Kantrowitz, Mr. Antol Herskovitz (medical photographer) and Dr. Hurwitt.

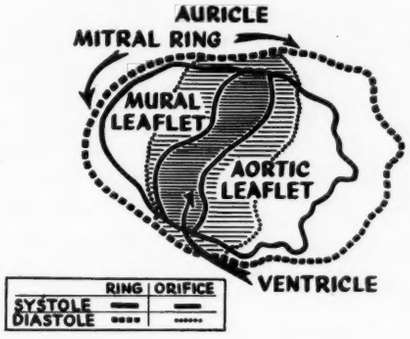
DR. ELLIOTT HURWITT: In 1517 a series of anatomical illustrations of the interior of the heart were demonstrated to His Holy Eminence, Cardinal Luis of Aragon, by Leonardo da Vinci. Da Vinci clearly depicted and visualized the chordae tendinae, the papillary muscles and the component parts of the anatomical features of the valves. In the four and a half centuries that have elapsed since this demonstration little has been added to our knowledge of the gross anatomy of these structures. Da Vinci speculated, with less accuracy, about how these structures worked; indeed, there is still no complete understanding of the function of these structures although there has been considerable theorizing, much of it highly controversial.

In 1923 Dr. Jacob Sarnoff of Brooklyn recorded photographically a few beats of the interior of the excised dog's heart. In 1950 Smith, Essex and Baldes of the Mayo Clinic conducted their remarkable study of the mechanism of the production of heart sounds. In this study dogs' hearts were excised, were kept beating with oxygenated Ringer-Locke's solution, generous incisions were made into both atria, and the mitral and tricuspid valves were visualized from their auricular surfaces as they opened and closed in diastole and systole.

In order for us to gain insight into the mechanism of action of these structures in the living animal it is necessary to obtain a bloodless field, and for this we have taken advantage of the mechanical heart devised by Dr. Adrian Kantrowitz at the Montefiore Hospital. This system differs from that of Dr. Gibbon, which is the prototype of most of the mechanical hearts employing an extracorporeal oxygenator, in that the dog's own lung oxygenates the blood. The oxygenated blood is picked up by cannulae inserted into the left pulmonary veins through the left auricular appendage; then it is carried to a vacuum auricle by suction, and propelled by a De Bakey roller-type pump to be reintroduced into the circulation by means of the femoral arteries, traveling retrograde up the aorta, and perfusing the coronary arteries, the cerebral arteries, and other vital structures. By means of this system it has been possible to maintain dogs and cats with the left side of the heart completely free of blood for periods up to a half hour. It is possible to make generous incisions into the left auricle and ventricle and to visualize the mitral valve from both aspects.

It must be emphasized that we have not achieved normal conditions. These are heparinized dogs, anesthetized with intravenous nembutal; the chest is open, eliminating normal intrapleural pressure; the auricle is open, eliminating normal auricular pressure; the aortic valve is maintained in a closed position by the pressure of the retrograde perfusion; only the right side of the heart is pumping blood; and fluid is not constantly present on both sides of the mitral valve as it normally is. In spite of these deviations from normal it is remarkable to see how much valvular and ring function actually takes

place. In diastole the valve ring and valve cups are open, despite the fact that the auricle is at atmospheric pressure and there is no fluid in the auricle. In systole, with the left auricle and ventricle empty of fluid, there is a rhythmic sphincter-like contraction of the entire mitral ring, narrowing considerably the size of the lumen which the mitral valve cusps must bridge to complete valvular closure. This is of considerable importance when we take up the subject of valvular surgery, because the size of the gap that has to be bridged is really much smaller than one would assume. It is made much smaller by this contraction of the valvular ring, which explains why a stenotic valve can function once a commissurotomy has been performed.



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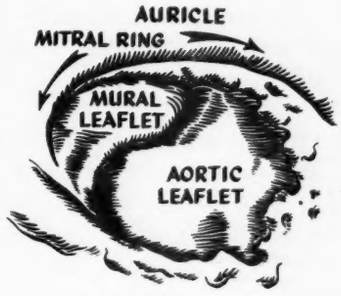

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FIG. 1. Diagram demonstrating changes in contour of valve ring and lumen in systole and diastole (muscular component).

FIG. 2. Drawing, from movie, of valve cusps in closed position (see text).

In Figure 1, the outer dotted line demonstrates the size of the valve ring in diastole and the inner dotted line indicates the size of the valve lumen. The solid lines show how much this ring actually closes in during systole, and how much narrower the orifice becomes; this is the entire size of the lumen that the cusps have to bridge.

Figure 2 shows the valve closed, revealing the smaller mural leaflet and the much larger aortic leaflet. Note how irregular and curved this commisure line is. This slide and the preceding slide were taken from frames in the "movie."

When we analyzed the pictures of the chordae tendineae, we noted that at the onset of each systole they show temporary slackening. This has to be so if you consider what happens in systole; as the distance between the apex and the base of the heart becomes shortened and the walls of the ventricles more closely approximate each other the chordae temporarily have to go slack.

We were able also to visualize the mitral valve in a number of instances after fluid had been added to the left ventricle; we then noted complete closure of the valve cups in addition to the sphincter action of the mitral ring. It is not necessary to have fluid present on the auricular side for the valve cusps to open but the valve cusps will not close unless fluid is present on the ventricular side. Again, let me emphasize the relative size of the two leaflets—the aortic leaflet is much larger than the mural. The valves do not meet on edge but actually roll over each other.

To summarize, under this set of abnormal conditions in which the chest is open, the auricle is open, and the left side of the heart is free of fluid, we have shown that there are two components of mitral valve function—a muscular component which enables the mitral ring to narrow with each cardiac systole, and a hydrodynamic component without which the valve cusps will not close but in the absence of which the valve leaflets will open. We have also shown that the chordae tendineae temporarily go slack at the onset of each systole.

DR. TURNER: Thank you, Dr. Hurwitt. When an obstruction develops at the mitral orifice, profound alterations result in the hemodynamics. These will be discussed by Dr. West.

DR. JOHN R. WEST: The hemodynamic changes associated with mitral stenosis, which have occupied the attention of physicians and physiologists for many years, have been the subject of renewed intensive study in the last few years in many institutions. This great activity is the result in part of the development of precise methods for studying the human circulation but has been given its greatest impetus by the

advent of an effective surgical treatment of this disease.

With few exceptions the hemodynamic studies of mitral valvular disease made in our laboratory have been performed on a selected group of patients, those who were being considered for valvular surgery because of disabling symptoms. This group is not, therefore, representative of the entire population with mitral disease, many of whom live normal lives with little or no cardiac disability.

The methods used in making the observations to be reported are familiar to all of you. Right heart catheterization was performed in the usual manner with the patient in a post-absorptive state. Determinations of cardiac output, intracardiac and intravascular pressures were made at rest and, in some patients, during non-strenuous leg exercise. While at rest the patients were lying in a comfortable position on a fluoroscopic table. Exercise was performed in the same position, the patient moving weighted pedals with his feet. Most of the patients were in a truly basal state at rest, and exercise in most instances was mild. In an attempt to achieve as steady a metabolic state during exercise as was present at rest we had the patients perform the exercise for eight to ten minutes as a rule and waited until exercise had been underway for at least five minutes before starting the collection of blood samples and expired air for determination of cardiac output. The pressures during exercise which are reported were taken either just prior to or just after the exercise cardiac output determination.

There were eighteen patients all told, nine with pure mitral stenosis, i.e., with an apical diastolic murmur only, and nine who were thought to have mitral insufficiency as well as stenosis, on the basis of the additional finding of an apical systolic murmur with the characteristic transmission. None of the patients presented clinical evidence of rheumatic activity at the time of study and in none were there signs of right ventricular failure. None of the patients with mitral insufficiency were thought to have significant enlargement of the left ventricle although the limitations of conventional electrocardiographic and roentgenologic technics in the detection of this are appreciated. The majority of the patients were fully digitalized.

In the tables the patients are grouped according to the valvular lesion, the cardiac rhythm, and in the order of estimated functional capacity using the criteria of the New York Heart Association. Of the nine patients with pure mitral stenosis four were males and five were females. The ages ranged from thirty-two to fifty-three years. Six had normal sinus rhythm and three had auricular fibrillation. The majority were considered to have significant limitation of physical activity, there being one in the New York Heart Association Class I, five in Class II, two in Class III and one in Class IV.

The observations made on these patients are tabulated in Table I. Only three patients (J. S., J. R. and A. At.) were found to have a normal cardiac index at rest if one discounts that of the patient (A. B.) who developed pulmonary edema during the procedure. The remainder were abnormally low. On exercise the cardiac index increased significantly (i.e., to a value 10 per cent greater than the resting level) in each of six patients, but only two (J. S. and J. R.) had what can be considered to be a normal increase in blood flow* commensurate with the increase in oxygen consumption over the basal value. These two patients increased the stroke volume with exercise; in the remainder the stroke volume decreased.

All but one of the patients had some degree of pulmonary hypertension at rest and in every instance an increase in the pulmonary arterial pressure was noted during exercise. All grades of pulmonary hypertension were observed. Measurements of right ventricular diastolic pressures during exercise or at rest were made, unfortunately, in only a few of these patients, not enough to warrant discussion. No significant changes were noted in the peripheral arterial pressure.

Even with this small series it is possible to draw certain tentative conclusions with respect to the relation of the hemodynamic and clinical findings. It is of interest to note, for example, that hemoptysis had occurred in six of nine patients but that its severity was not a good indication of the degree of pulmonary hypertension found at the time of study. Dyspnea on exertion was a real complaint of all patients except one (J. S.) and, in general, those most incapacitated by this symptom had the greatest

* A normal individual, undergoing a test of this sort, will increase his cardiac output by more than 600 or 700 cc. for every 100 cc. increase in oxygen consumption over the basal amount. (Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Cournand, A. and Richards, D. W., Jr. Hemodynamic studies in rheumatic heart disease. *Circulation*, 6: 688, 1952.)

degree of pulmonary hypertension. There was one notable exception, however; patient M. D. who had extreme pulmonary hypertension, had only mild to moderate dyspnea on exertion and complained chiefly of "weak spells" or giddiness which was also present occasionally at rest. Since all but two of the patients had been digitalized for one reason or another before the study, nothing should be said here concerning the effect of this medication, but I will speak of this matter in a moment. Finally, there did not seem to be a clearly defined difference in the

TABLE I

CLINICAL AND HEMODYNAMIC FINDINGS IN NINE PATIENTS WITH MITRAL STENOSIS†

Patient	Vent.	O_2 Cons.	A-V Diff.	C.I.	H.R.	S.V.	Pressure, mm. Hg: Pulmonary Artery s/d, m	Pressure, mm. Hg: Systemic Arteries s/d, m	Remarks
J. S., male, 42 yr. R	4.1	129	4.5	2.87	58	85	20/6 12	104/55 75	NSR. Never in failure. No hemoptyses. No digitalis. No dyspnea except on very strenuous exertion. Class I.
BSA = 1.72 E	7.3	300	7.4	4.16	79	88	34/11 20	129/70 79	
J. R., male, 48 yr. R	5.6	143	5.1	2.81	64	76	31/21 24	110/61 81	NSR. Never in failure. Large hemoptyses. No digitalis. Mild exertional dyspnea. Class II.
BSA = 1.74 E	7.7	251	6.8	3.70	72	89	52/29 39	122/67 88	
A. At., female, 39 yr. R	3.5	120	4.2	2.84	77	66	39/23 30	118/73 92	NSR. Previous cardiac failure. No hemoptyses. Digitalis. Mild exertional dyspnea. Class I.
BSA = 1.78 E	5.7	220	6.8	3.24	96	60	62/30 45	128/75 97	
M. R., female, 32 yr. R	4.4	123	4.7	2.61	76	50	47/21 32	123/77 97	NSR. Previous cardiac failure. Rare small hemoptyses. Digitalis. Moderate exertional dyspnea. Class II.
BSA = 1.45 E	6.2	167	....	....	88	..	81/40 53	131/79 102	
M. D., female, 34 yr. R	5.1	144	6.3	2.29	96	38	105/56 74	105/66 81	NSR. Never in failure. Rare small hemoptyses. Digitalis. Moderate exertional dyspnea. Class III.
BSA = 1.61 E	....	...	8.0	....	111	..	128/67 88	103/73 83	
A. B., female, 45 yr. R	6.2	163	5.7	2.86	109	39	117/55 80	123/70 95	NSR. Previous cardiac failure.* Rare small hemoptyses. Digitalis. Severe exertional dyspnea. Class IV.
BSA = 1.49 E	....	...	....	....	..	..	....	....	
G. S., male, 46 yr. R	4.2	147	5.6	2.63	85	55	37/19 29	132/84 102	Auricular fibrillation. No hemoptyses. Digitalis. Never in cardiac failure. Moderate exertional dyspnea. Class II.
BSA = 1.77 E	7.8	319	10.9	2.93	114	46	53/29 41	137/88 109	
S. F., male, 43 yr. R	4.9	138	7.1	1.94	58	58	48/25 33	111/69 86	Auricular fibrillation. Previous cardiac failure. Several small hemoptyses. Moderate exertional dyspnea. Digitalis. Class II.
BSA = 1.73 E	10.5	261	10.9	2.39	81	51	78/41 54	120/73 87	
E. B., female, 53 yr. R	3.8	143	7.5	1.91	68	43	46/22 30	126/75 93	Auricular fibrillation. Previous cardiac failure. One large hemoptysis. Digitalis. Moderate exertional dyspnea. Class III.
BSA = 1.52 E	7.4	208	9.2	2.26	97	35	76/40 53	141/90 105	

* This patient developed mild pulmonary edema during the procedure.

† The meaning of the abbreviations are as follows: BSA = body surface area in square meters; R = at rest; E = during exercise; Vent. = pulmonary ventilation in L. per minute per square meter of body surface at body temperature, ambient pressure, saturated with water vapor; O_2 cons. = oxygen consumption in cc. per minute at 0°c., 760 mm. Hg, dry; A-V diff. = arteriovenous difference for oxygen expressed as volumes per cent; C.I. = cardiac index in L. per minute per square meter of body surface; H.R. = heart rate; S.V. = stroke volume in cc.; s/d, m = systolic/diastolic, mean. NSR = normal sinus rhythm. For discussion see text.

Only two patients (A. B. and S. F.) had had clear cut episodes in the past of pulmonary edema occurring spontaneously, i.e., not associated with acute rheumatic fever, pulmonary infarct, pneumonia, etc. These patients had moderate to severe elevation in resting pulmonary arterial pressure. Five of the nine patients had had ankle edema or hepatic engorgement at one time or another in the past, indicated on the slide as "previous cardiac failure." Of these, three (A. At., M. R. and A. B.) had normal sinus rhythm, and two (S. F. and E. B.) had auricular fibrillation at the time of study. The cardiac output and pulmonary arterial pressure found in these patients did not serve to differentiate them from the four remaining patients who had never had congestive heart failure. hemodynamic pattern found in patients with auricular fibrillation as contrasted with that found in patients with normal sinus rhythm. A difference might certainly be expected but a much larger series than this would be required to demonstrate it in view of the many other variables that were present.

Of the nine patients who had mitral insufficiency as well as stenosis, two were males and seven females, and ages ranged from twenty-four to forty-four years. Four had normal sinus rhythm and five had auricular fibrillation. These patients were generally somewhat more incapacitated by their disease than were those with pure mitral stenosis but this is doubtless just a matter of chance. Three patients were placed in Class II, four in Class III and two in

Class IV. The observations pertaining to these patients are tabulated in Table II.

In only one instance was the cardiac index normal at rest, and this in a patient (E. S.) who was moderately apprehensive and was not thought to be in a basal state. In the remainder, no abnormalities in peripheral arterial pressure were noted and insufficient observations of right ventricular diastolic pressure were made.

The relationship between clinical and physiologic findings was essentially the same as had been found in the cases of pure mitral stenosis.

TABLE II

CLINICAL AND HEMODYNAMIC FINDINGS IN NINE PATIENTS WITH MITRAL STENOSIS AND MITRAL INSUFFICIENCY†

Patient		Vent.	O_2 Cons.	A-V Diff.	C.I.	H.R.	S.V.	Pressure, mm, Hg: Pulmonary Artery s/d, m	Pressure, mm, Hg: Systemic Arteries s/d, m	Remarks
E. S., male, 36 yr.	R	5.3	172	6.4	2.69	66	77	70/29 42	106/60 75	NSR. Previous cardiac failure. Large hemoptyses. Digitalis. Mild exertional dyspnea. Class II.
BSA = 1.89	E	....	...	....	....	..	..	....	....	
E. C., male, 24 yr.	R	4.8	121	7.0	1.73	79	37	74/43 55	111/75 88	NSR. Never in failure. Large hemoptyses. No digitalis. Mild exertional dyspnea. Class II.
BSA = 1.70	E	11.8	372	12.6	2.95	112	45	117/67 84	134/84 104	
H. C., female, 44 yr.	R	3.6	118	5.0*	2.37	85	46	48/24 31	120/73 93	NSR. Previous cardiac failure. No hemoptyses. Digitalis. Moderate to severe exertional dyspnea. Class III.
BSA = 1.65	E	5.6	186	7.9*	2.35‡	119	33	....	138/79 100	
B. K., female, 44 yr.	R	4.5	128	7.3	1.76	85	30	90/29 49	119/68 86	NSR. Previous cardiac failure. No hemoptyses. Digitalis. Severe exertional dyspnea. Class IV.
BSA = 1.43	E	....	...	....	....	..	..	....	....	
E. G., female, 40 yr.	R	2.6	118	5.4	2.19	68	55	24/10 15	156/83 108	Auricular fibrillation. Never in failure. No hemoptyses. Digitalis. Mild exertional dyspnea. Class II.
BSA = 1.71	E	6.4	256	....	....	90	..	38/18 27	158/90 114	
V. H,, female, 30 yr.	R	4.2	140	6.7	2.08	58	51	32/16 20	114/73 89	Auricular fibrillation. Never in failure. No hemoptyses. Digitalis. Moderate exertional dyspnea. Class III.
BSA = 1.41	E	5.7	207	8.2	2.52	92	39	67/40 43	121/82 100	
A. Ad., female, 37 yr.	R	3.3	110	7.6	1.44	90	22	24/14 17	114/78 91	Auricular fibrillation. Previous cardiac failure. No hemoptyses. Digitalis. Moderate exertional dyspnea. Class III.
BSA = 1.40	E	9.9	269	14.2	1.89	160	16	44/28 37	....	
L. A., female, 25 yr.	R	4.4	160	6.4	2.50	88	47	32/20 25	129/72 90	Auricular fibrillation. Previous cardiac failure. Occasional small hemoptyses. Digitalis. Moderate to severe exertional dyspnea. Class III.
BSA = 1.65	E	5.8	203	7.5	2.70	99	45	50/29 37	134/77 98	
R. D., female, 42 yr.	R	4.4	141	7.3	1.94	73	42	83/40 54	114/72 88	Auricular fibrillation. Previous cardiac failure. No hemoptyses. Digitalis. Severe exertional dyspnea. Class IV.
BSA = 1.57	E	9.0	251	12.9	1.95	129	24	121/69 87	123/87 100	

* Mixed venous sample secured in right auricle.

† The meaning of the abbreviations are as follows: BSA = body surface area in square meters; R = at rest; E = during exercise; Vent. = pulmonary ventilation in L. per minute per square meter of body surface at body temperature, ambient pressure, saturated with water vapor; O_2 cons. = oxygen consumption in cc. per minute at 0°c., 760 mm. Hg, dry; A-V diff. = arteriovenous difference for oxygen expressed as volumes per cent; C.I. = cardiac index in L. per minute per square meter of body surface; H.R. = heart rate; S.V. = stroke volume in cc.; s/d, m = systolic/diastolic, mean. NSR = normal sinus rhythm. For discussion see text.

‡ Cardiac index during exercise was measured *during* the fifth minute of exercise in the case of patients H. C. and A. Ad.

the cardiac index was lower than normal. Determinations of cardiac index during exercise were made in six cases and a significant increase over the basal level was noted in only three (E. C., V. H. and A. Ad.); in none of these, however, was there a normal increase in blood flow in relation to the increase in oxygen consumption. The stroke volume decreased with exercise in every instance but one (E. C.). All but one of the patients had pulmonary hypertension at rest and all of those tested had an increase in pressure during exercise. All degrees of pulmonary hypertension were found. As with the patients who had mitral stenosis alone, Hemoptysis, which had occurred in three cases, was a poor guide to the degree of pulmonary hypertension. Dyspnea on exertion was noted by every patient, and in two (B. K. and R. D.) who had severe pulmonary hypertension at rest dyspnea was present sometimes at bed rest. Two others (E. S. and E. C.), however, who had just slightly less severe pulmonary hypertension at rest, complained only of mild dyspnea on exertion. The previous occurrence of congestive heart failure was noted in six of the nine patients but this again was not related in any way to the severity of the hemodynamic alterations at the time of study nor to the presence or

absence of auricular fibrillation. Finally, there was no definite difference in the pattern of dysfunction, as defined by these few studies, between our patients with pure mitral stenosis and those with additional mitral regurgitation. A larger series, perhaps, might bring out differences, as might studies of patients with minimal degrees of stenosis and well marked mitral insufficiency. Anatomically established cases of the latter type are not common and I have not seen studies of such cases reported in the literature.

To conclude this aspect of our discussion, it is apparent that mitral stenosis with or without (clinically) minor degrees of mitral insufficiency can be associated with striking circulatory abnormalities. The trend of these disturbances is toward increased pulmonary vascular pressure on the one hand and decreased cardiac output on the other. It is apparent that the end result is subject to great variation from patient to patient. Thus there are patients with little or no circulatory change demonstrable by our technics while at the other end of the scale there are those in whom the pulmonary arterial pressure approaches or exceeds that of the systemic arteries and cardiac output is extremely low and seemingly fixed.

Let us consider for a moment the various factors which are responsible for these hemodynamic changes and discuss the manner in which they work. To simplify, one can say that there are three main pathologic features of mitral valvular disease which must be considered. These are: (1) the valvular deformity itself, (2) pulmonary atherosclerosis and arteriolosclerosis which occurs not infrequently in long-standing cases and (3) the state of the ventricular myocardium. It is convenient to discuss each of these factors separately.

The Valvular Deformity. Under given conditions of differential pressure between the atrial and ventricular sides of the mitral valve the rate of blood flow from atrium to ventricle during diastole will depend upon the size and shape of the valvular orifice. The relationship of *orifice configuration* to rate of flow is doubtless complex and I am not in a position to discuss it today. The general effect, however, of *orifice size* on flow is fairly obvious, i.e., the smaller the orifice the smaller is the rate of flow under, to repeat, fixed conditions of pressure differential. Conversely, a constant flow will be maintained through any orifice of decreasing size only if the pressure differential on the two sides of the orifice is increased. These simple physical principles are important but are not the only determinants of the ultimate readjustment of human circulation to a mechanical block at the mitral valve. One must consider also the various factors which tend to maintain cardiac output at a normal level as well as the actual nature of blood flow through the valve.

The cardiac output of a normal adult under basal conditions will generally lie somewhere between 2.8 and 3.5 L. per minute per square meter of body surface area and the arteriovenous difference for oxygen will be around 4 or 5 volumes per cent. This fairly narrow range of normal for cardiac output and arteriovenous difference is doubtless the result of many different mechanisms which will continue to function whether or not mitral stenosis is present. As a result, the theoretic possibility that a severe degree of mitral stenosis might exist without any degree of pulmonary hypertension is seldom, if ever, realized since cardiac output always seems to be maintained at a level above that to which, in theory, it could fall and still be compatible with life. The cardiac output in severe mitral disease is *lower* than normal, it is true, but at the same time the pulmonary arterial pressure (and, presumably, left atrial pressure) is generally abnormally high. The increase in left atrial pressure under these circumstances should not be considered a compensatory response whereby the cardiac output is bolstered simply because it can be deduced that a greater flow will occur when there is a greater pressure differential across the valve. The increased left atrial pressure is, rather, the result of various regulatory mechanisms working in the face of an impaired mechanism of left atrial emptying. The fact that mitral stenosis *per se* is one of these regulating mechanisms, because of its effect upon left ventricular output, does not alter this concept but actually aids in understanding why output is low.

The mechanisms whereby mitral stenosis of a degree sufficient to interfere significantly with left atrial emptying may result in pulmonary hypertension and reduced cardiac output are thus readily understood. Less apparent probably are the factors which determine whether a particular degree of stenosis will interfere with effective left atrial emptying or will be associated with essentially normal hemodynamics. In this connection, consider for a moment the normal

mitral valve. The orifice of this valve is quite large during diastole and offers little impedance to the flow of blood from atrium to ventricle. It is so large, in fact, that it can, theoretically, be substantially reduced in size without materially increasing the resistance to the flow of blood. Furthermore, it has been shown in the dog that with a normal ventricular rate and a normal degree of tonus of the muscle fibers, ventricular filling is complete, or almost so, well before the beginning of systole. This implies that the flow of blood from atrium to ventricle is more rapid early in diastole than in the latter portion, which accounts for the fact that reductions in the diastolic filling period can occur as, for example, during exercise, without a decrease in stroke volume or even with an increase.

The large size of the normal orifice together with this discontinuous flow from atrium to ventricle probably accounts for the fact that certain degrees of mitral stenosis can be present and yet result in no interference in *effective* left atrial emptying, although the flow from atrium to ventricle may not follow the normal pattern of rapid early phase and slower late phase. The degree of stenosis will, of course, determine to what extent the diastolic filling period can be shortened without affecting blood flow. Thus there are patients who have no significant quantitative interference with left atrial emptying whether the heart rate is fast or slow, others in whom impairment is noted only during tachycardia, and some, like most of the patients in this series, in whom the damaged mitral valve seems to impede left atrial emptying even at slow heart rates.

Changes in the Pulmonary Vascular Bed. It is not uncommon to find, in long-standing cases of mitral valvular disease, varying degrees of pulmonary atherosclerosis as well as intimal sclerosis of the smaller arteries and precapillary vessels. The latter change, when severe, can effectively increase the resistance to blood flow offered by these smaller pulmonary arterial branches, and, in a manner analogous to that in systemic hypertension, result in an elevated pressure in the pulmonary arteries. Atheromatous changes in the larger branches of the pulmonary artery, just like atheromatous changes in the aorta and great systemic vessels, will decrease the elasticity of these vessels and will thereby tend to increase the pulse pressure.

Along with most other workers, we believe that vascular changes such as these often make a significant contribution toward the more severe degrees of pulmonary hypertension which are found in many cases of advanced mitral disease. Some investigators believe, in addition, that the precapillary vessels sometimes undergo active vasoconstriction and have cited as evidence favoring this view the fact that an increase in pulmonary arterial pressure can occur during exercise without an increase in cardiac output. Others have advanced the more plausible view that this phenomenon is due to a temporary inequality in the output of the two ventricles occurring at the beginning of exercise, that of the right exceeding that of the left, with a resultant engorgement of the pulmonary vascular bed lasting for the duration of the exercise. The limiting factors in this situation are, of course, the same as we have discussed previously, e.g., the effect of heart rate upon left auricular emptying and left ventricular output, the competence of the right ventricle, venous return, etc.

The next two figures may illustrate some of these points. The first, (Fig. 3A), graphically sums up the hemodynamic findings in the case of R. D. Note that cardiac index during exercise was exactly the same as that at rest while pulmonary arterial and "pulmonary venous" pressure showed a substantial rise along with an increase in heart rate. Figure 3B reproduces photographs of pressure records made in this case which show the variation in "pulmonary venous" pressure* coincident with moment to moment variations in heart rate during a reasonably steady state of exercise. If this "pulmonary venous" pressure truly reflects left atrial pressure, this figure affords a good illustration of the effect of heart rate upon left atrial emptying.

The State of the Myocardium. Left ventricular failure from any cause will result in elevation of left atrial and pulmonary arterial pressure whether or not there is mitral stenosis. The group on the Columbia Division at Bellevue Hospital have reported patients with mitral stenosis who responded to acute digitalization in a manner similar to that of patients in left ventricular failure from hypertension or other heart disease, i.e., with an increase in cardiac output and a decrease in pulmonary arterial pressure, without significant change in heart rate, indicating that the relief of pulmonary

* Hellems, H. K., Haynes, F. W. and Dexter, L. Pulmonary "capillary" pressure in man. *J. Applied Physiol.*, 2: 24, 1949.

congestion in these cases was due to better left ventricular emptying. Similarly, there is little reason to doubt that the intense pulmonary congestion seen in some patients with mitral stenosis who have severe active carditis is, at least in part, a result of impaired left ventricular emptying.

part to disease of the right ventricle which has reduced this chamber's ability to respond to a work load.

Thus in the analysis of factors responsible for the hemodynamic alterations found in a patient with mitral valvular disease, in addition to the mechanical disturbance produced by the dis-

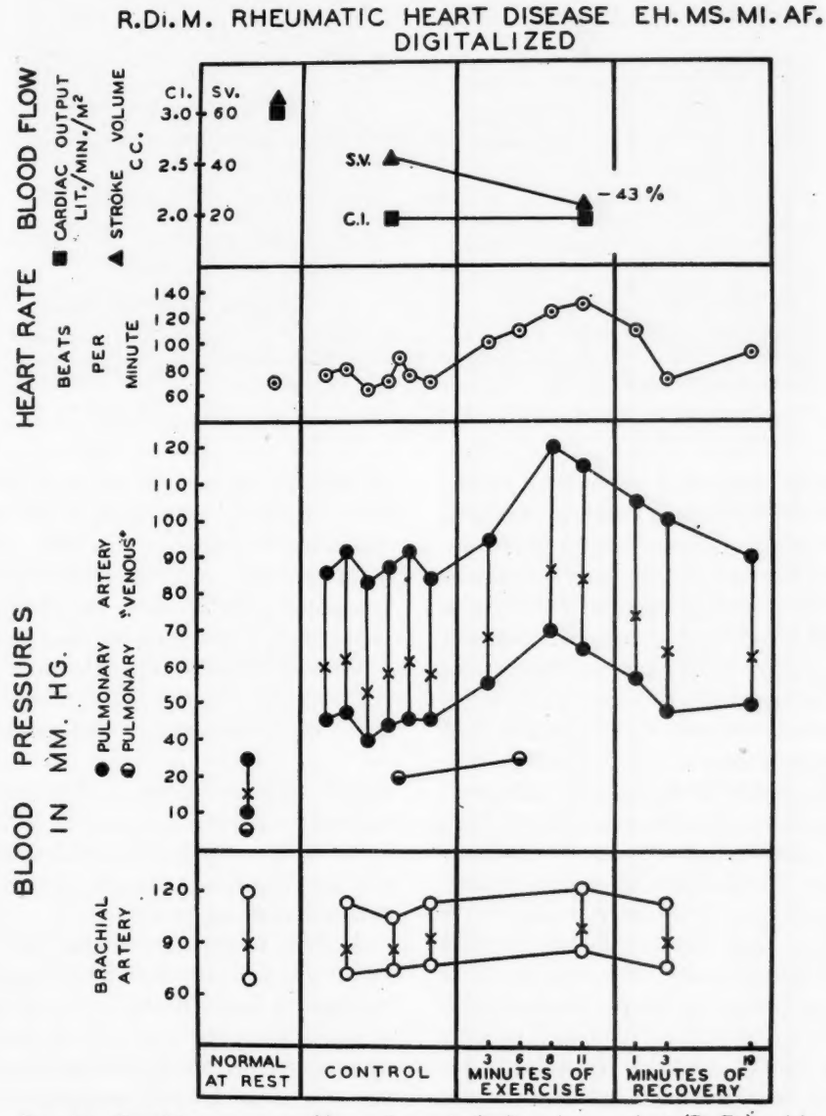


FIG. 3A. Graphic summary of hemodynamic findings in a patient (R. D.), with rheumatic heart disease with mitral stenosis and mitral insufficiency. For discussion see text.

Disease of the right ventricular myocardium, on the other hand, will doubtless affect the action of that chamber. It seems likely, therefore, that some of the extremely low cardiac indices and relatively low pulmonary arterial pressures observed in the presence of what seems to be a tight mitral stenosis are due in

eased valve itself and the secondary pulmonary vascular changes, the possibility of faulty action of the right or left ventricle or both must always be borne in mind.

DR. TURNER: Thank you, Dr. West. From Dr. West's discussion it has become evident that mitral stenosis may produce such a severe dis-

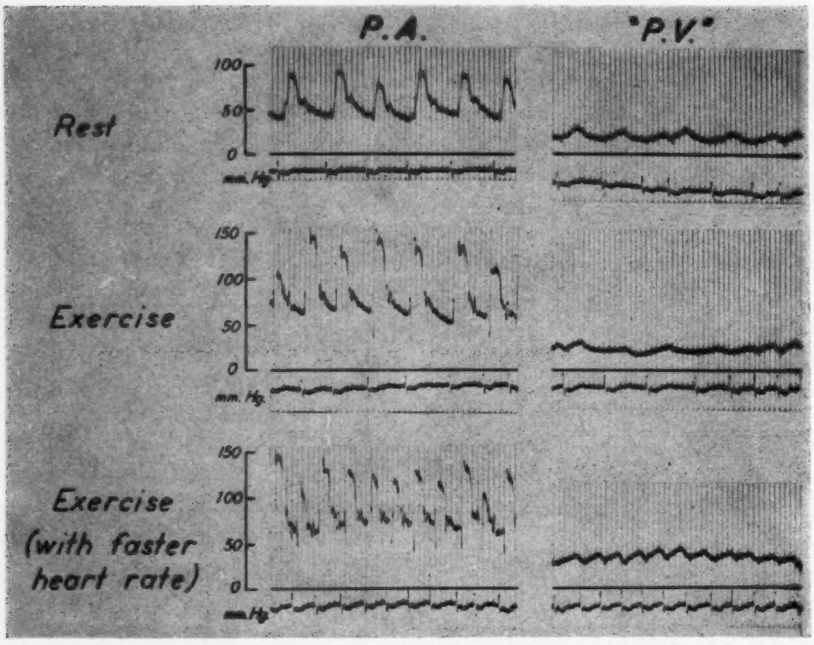


FIG. 3B. Photographs of pressure records obtained in the patient (R. D.) whose findings are summarized in Figure 3A. For discussion see text.

order in cardiac function that one may, I think, quite fairly ask whether every patient in whom mitral stenosis develops should not be given the benefit of surgical correction, if surgery is possible.

The answer to that question is "Yes" in a number of clinics today. I think our position here is considerably more conservative than that. We cannot overlook the fact that many patients with mitral stenosis do extremely well for years. In a recent issue of *Circulation*,* there is a most interesting report by Bland and Jones on a series of 1,000 patients with rheumatic fever who were followed a minimum of twenty years and some thirty years. At one time or another about 800 of these patients developed evidence of heart involvement and about 200 apparently escaped. Of the whole series, 300 were dead at the end of twenty years. Eighty per cent of these had died of rheumatic fever or heart failure, 10 per cent had died of subacute bacterial endocarditis and the remainder from a variety of causes. This is, again let me say, in twenty years. Of the 700 survivors, only 1 in 4 had any limitation of activity. Finally, of 117 patients with so-called pure mitral stenosis, 13 died within twenty years and 12 of the survivors had developed symptoms that resulted in limitation of activity. It would seem to follow that not every patient with mitral stenosis should be subjected to surgery, but only those who show evidence of progressive disability: increasing symptoms, increasing heart size, increasing pulmonary hypertension, and so forth.

Our criteria for the selection of patients are certainly in a state of flux. We hope to establish them more reasonably and more successfully as we learn from experience. In a random way, I should like to mention a few points to be considered in selecting a patient for operation.

1. As already stated, evidence of progressive cardiac disability should suggest serious consideration of surgery.

2. Preferably, we believe, the patient should be between twenty and forty years of age. Above the age of forty the technical difficulties for the surgeon increase and the patients are poorer operative risks. In the younger age groups, below the age of twenty, the possibility of active rheumatism is always greater.

3. There should be no evidence of rheumatic activity. We should make our mistakes in considering fever and an elevated sedimentation rate as due to rheumatic activity when they are not, rather than in arbitrarily deciding that they are due to some other cause.

4. It is hardly necessary to state that you would certainly not consider a patient who might have a superimposed bacterial endocarditis.

* BLAND, E. F. and JONES, T. D. Rheumatic fever and rheumatic heart disease. A twenty year report on one thousand patients followed since childhood. *Circulation*, 44: 836, 1951.

5. The mitral valve alone should be involved. In this connection one of the most troublesome decisions one has to make concerns a soft diastolic murmur heard in the aortic area in patients who have mitral stenosis. Without enlargement of the left ventricle, with, as I said, a soft murmur, and with a change in that murmur with respiration or change in position, I think there is reasonable doubt as to true aortic valve involvement; in other words, it may be the so-called Graham Steele murmur. If there is definite evidence of aortic valve involvement, the patient is not a candidate for mitral commissurotomy.

6. As concerns the mitral valve, theoretically and probably in fact, the patients with so-called pure mitral stenosis will do better than those who have some mitral insufficiency as well. The difficulty comes in the diagnosis of mitral insufficiency. There is, in my mind at least, a very real question whether the presence of a systolic murmur, or at least the characteristics of the systolic murmur, enables one to state with any accuracy the degree of insufficiency present. There are ancillary measures that may be adopted in our effort to differentiate the insufficiency from stenosis but their interpretation is not entirely clear and I do not think it would be profitable to go into them here.

7. Cardiac failure *per se*, we believe, is not a contraindication to mitral commissurotomy but it is when the failure cannot be controlled by the usual means.

8. We do not consider auricular fibrillation a contraindication.

9. A history of emboli is not a contraindication.

10. A history of hemoptysis we consider rather an indication than a contraindication, despite the lack of close correlation between the degree of elevation of pulmonary artery pressure and the occurrence of hemoptyses.

11. There should certainly be no appreciable left ventricular hypertrophy by x-ray. Granted, one cannot always tell from x-ray and fluoroscopy whether or not left ventricular hypertrophy is present, but if it seems to be clearly evident one should certainly consider either that a significant degree of mitral insufficiency is present or that there is aortic valvular disease, or both.

12. The electrocardiogram is helpful because the patients who show evidence of marked myocardial damage, presumably the result of rheumatic myocarditis, are probably poor risks. The thing one would like to see in the electrocardiogram is right axis deviation. That means that probably pure mitral stenosis is present, without significant disease of the aortic valve and without marked mitral insufficiency.

Now, when operation is considered desirable and the surgeon enters the case, for what he does and how he does it we shall hear from Dr. McAllister.

DR. FERDINAND F. MCALLISTER: One of the most exciting developments in medicine in the past ten years has been the successful treatment of mitral stenosis by surgical means. In 1902 it was suggested by Brunton that a direct attack upon a stenotic mitral valve might be achieved surgically. In the nineteen twenties this was attempted ten times by Cutler and Beck, Pribam, Souttar, Allen and Graham. Of the ten patients eight succumbed to the operative procedure and two survived. Of the two who survived one had a negligible cut in the mitral valve, was very little improved and died in four and a half years in cardiac failure. The other patient, a patient of Souttar, an English surgeon, was subjected to a dilatation of the stenotic mitral valve by a procedure which was almost identical with our present procedure of finger fracture. A purse-string suture was placed about the auricular appendage, a finger introduced into the heart, and the mitral valve palpated and dilated, just as we do now in finger fracture. This patient was said to be slightly improved but the follow-up reported was only three months.

After World War II surgeons again began to try to attack the mitral valve, perhaps stimulated by the efforts of Smithy to undertake surgery for the aortic valve. Two groups of workers became busy on this problem, one in Philadelphia, consisting of Drs. Bailey, Glover and O'Neill, and the other in Boston, headed by Dr. Dwight Harkin. Their first efforts were discouraging and they met with many failures. Soon, however, we began to hear reports of successful cases and, as time went on, it became more and more apparent that a successful means of dealing with the stenotic mitral valve might now be available in certain selected cases.

Why did these men succeed where others in the twenties had failed? True, we have had improvement in surgical technics, in pre- and postoperative support and in anesthesia with the open chest. But they succeeded more because

of an understanding of certain basic facts related to stenosis of the mitral valve. I would like to list these facts for you.

Number one is that acute mitral insufficiency is not well tolerated. It is not well tolerated in the normal dog, nor is the creation of an insufficiency over and above that which already exists in mitral valvular disease well tolerated. This is well illustrated by some experiments we did in dogs several years ago. Pressures were recorded from the left auricle immediately before and after experimental mitral valvulotomy. In two dogs the pressure rose from 50 to between 200 and 300 mm. of water. A third animal survived, which was very unusual; it is of interest that the lesion was on the mural leaflet not too far from the lateral margin. After ten months a section of the aortic leaflet was removed by punch biopsy and, surprisingly, the animal showed only a moderate rise in left auricular pressure. The pressure measurements, made with a water manometer, were as follows: the right auricular pressure rose from about 50 to 140 mm.; the left auricular pressure rose to 200 immediately after valvulotomy, and ten months later, had risen to 400 mm.; the values for the pulmonary artery pressure were: control 200, immediately after valvulotomy 300, and ten months later almost 500 mm.

It is of interest that the pressure gradient—and again I stress that these are just crude measurements with a water manometer—from the pulmonary artery to the left auricle was 145 mm. of water at the start and, after the creation of a valvular defect, this gradient of pressure was reduced to 90 immediately and it remained low, that is, 85, after ten months. With such a reduction in pressure gradient, pulmonary blood flow is, of course, greatly slowed. These data indicate that the creation of acute mitral insufficiency is very poorly tolerated.

A second fact which these workers realized was that there is a difference in the function of the valve leaflets. This has already been mentioned by Dr. Hurwitt. The aortic leaflet is considerably larger than the mural leaflet and through part of its origin is contiguous with the origin of the aorta. In the closed position it is this leaflet which overlies most of the left ventricular chamber and, as such, it is responsible for deflecting much of the blood into the aorta. This action has been called by Harkin the baffle action of the aortic leaflet of the mitral valve. Realizing this, Harkin developed a theory of the creation of "selective mitral insufficiency." He figured that since the aortic leaflet was so important in deflecting the blood into the aorta, if one were to try to dilate or enlarge a stenotic mitral valve it would be far better to deal with the mural leaflet than to disturb the aortic leaflet. From that it was only a step for him to conceive the idea that it would be even better to attack the leaflets at their lateral margins or commissures rather than near their centers.

A third set of facts deals with the pathology. It was noted by the Philadelphia group that much of the fibrosis and hardening in mitral stenosis occurs at the edge of the valve leaflets, and that frequently the body and the base of the leaflets are free and pliable. Further, they noted that the valves became fused at their lateral margins by little bridges and these fusion bridges began at the edges, worked centrally and were responsible for much of the narrowing which occurs in mitral stenosis. Hence it seemed apparent to them that if these fusion bridges could be ruptured or cut, they could not only enlarge the stenotic mitral ring without increasing any regurgitation which might exist but they might actually decrease regurgitation by permitting the valves to flap to a limited extent. Thus the operation of division of the commissures was developed.

Understanding these facts, we now approach the patient for surgery. Dr. Turner has taken up the indications and contraindications, with which I might say I am in complete accord. The preoperative preparation of the patient is distinctive in just a few ways. In the first place, the patient has to be at the peak of compensation. In the second place, if there is a red cell mass deficit or if the total blood volume is not quite up to the estimated normal, it is probably wiser not to disturb the patient's hemodynamic state by attempting to achieve normal levels with blood transfusions, and so on. In other words, if the patient is compensated it is probably better to let him alone and not disturb him prior to operation.

The anesthetization of these patients is hazardous and constitutes one of the greatest risks of the procedure. The induction period is particularly difficult because it is necessary to achieve a fair depth of anesthesia in order to introduce an intratracheal tube. Here, we have managed to devise a system using ethylene for induction and for the intubation and then

switching to light ether to carry the patient through the remainder of the operation.

The patient is placed on the right side and the chest is entered through the left fourth intercostal space. The pericardium is opened and the left auricular appendage and the heart present themselves.

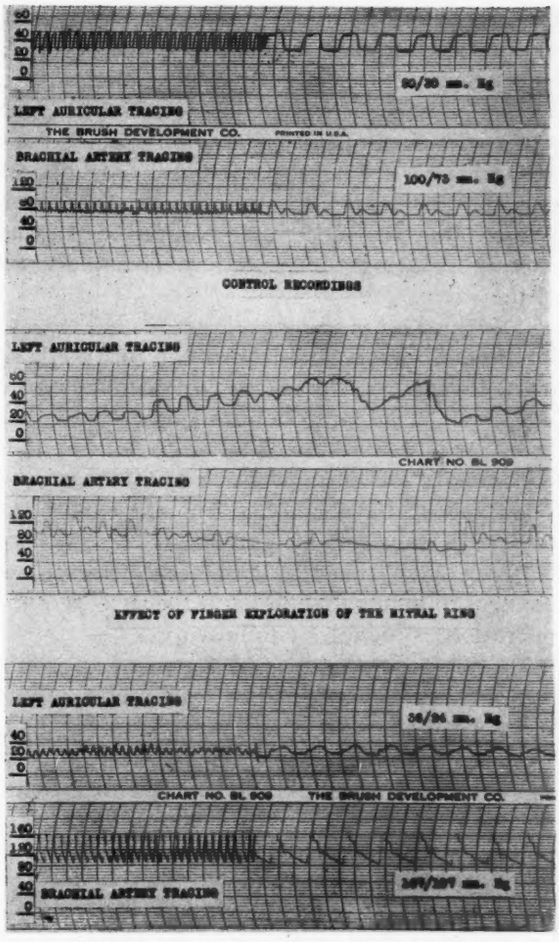
If there has been a history of emboli or if it appears that there is a clot within the auricular appendage, it is my belief that it is wisest to try to allow the blood from within the heart to flush this clot out with the least possible disturbance of the auricular appendage. This can be done by placing a clamp at the base of the auricular appendage, without closing it, and then excising a small amount of the tip of the appendage to allow hemorrhage to ensue. This will flush out any loose clots which may be within the auricle and then the clamp can be quickly driven home. I think this is perhaps safer than applying the clamp first, which might divide or crush some fragment of clot and thus liberate it into the circulation. After the clamp has been applied a purse-string suture may be placed about the base of the appendage.

The opening in the auricular appendage is then enlarged enough to permit introduction of the right index finger and, as the finger is introduced, the clamp is released and the purse-string drawn snug. The finger is now an exploring one. One can feel clots and one may actually feel a jet of regurgitation, if such exists. With practice the surgeon may be able to estimate the degree of mitral insufficiency.

The finger is then passed down into the funnel toward the stenotic mitral valve. If you will place the right index finger into the button hole of your coat, you will get some idea of how the stenotic mitral valve feels.

The commissures are next identified and gentle to moderate pressure is applied against the anterior commissure. If this fractures easily, the fracture should quickly be taken advantage of and a tear produced to the rim of origin of the valve. This fracture may result in an adequate opening. If a one-and-a-half to two finger-breadths' opening is produced, I think this is probably adequate; but if less than that is achieved, I think it is desirable to try to fracture the posterior commissure. In the event that moderate pressure fails to produce any type of fracture one should not persist in trying to force it. In that case one of the many different knives which have been designed for the procedure

M.D. Mitral Commissurotomy



Recording Following Commissurotomy

FIG. 4. Pressure recordings (Lilly manometer) from the left auricle and brachial artery of a patient with mitral stenosis before, during and after mitral commissurotomy.

should be introduced and a cut started at the commissure and extended further by fracture.

The danger of rupturing the aortic leaflet by forcible dilatation and fracture cannot be overemphasized.

After the fracture or cutting of the commissure has been achieved the finger is then withdrawn and the purse-string suture at the base of the auricular appendage is drawn snug.

We have been interested in trying to measure some of the changes in pressure in the left auricle, pulmonary artery and peripheral circuit which occur during the procedure of commissurotomy. We have very little data on this as yet but I would like to present some of it.

Figure 4 is a recording of pressure made with the use of fine plastic catheters introduced into

one of the pulmonary veins and threaded into the left auricle; there is a simultaneous recording of pressure from a brachial artery. Both records were obtained with the Lily electric manometer. While the finger is exploring the mitral ring the left auricular pressure rises and the systemic arterial pressure falls, exactly as you would expect. One reason for showing this is to emphasize that too much time cannot be allowed to elapse during the procedure of exploration of the valve.

The third set of tracings shows the left auricular pressure after commissurotomy, in this case a finger fracture. The pressure has dropped from 50/30 to 36/24 and simultaneously there has been a rise in systemic arterial pressure with a widening of the pulse pressure.

As yet we have not had enough experience to decide what sort of correlation there will be between the magnitude of the immediate changes in hemodynamics and the success of the operation as judged by follow-up.

In the postoperative management it is important not to overload the circulation with blood or fluids and it is desirable to have the patient regulate his own fluid balance in so far as this is feasible. To that end every effort should be made to eliminate intravenous therapy as soon as possible and to start the patient on by-mouth feedings when tolerated.

There are a few complications which should be stressed. One of these is the discharge of emboli into the circulation. In the experience of the Swedish workers, who have now done over a hundred cases of finger fracture of the mitral valve, this has been the chief cause of death. At Montefiore Hospital there has been one saddle embolus which immediately followed valvulotomy.

Another complication is the collapse which these patients sometimes show and which presents a difficult problem as far as treatment goes. This may represent a central cardiac collapse without pulmonary edema. Under such conditions, it may be unwise to give the patient a transfusion although one may be sorely tempted to do so.

For the results of this type of surgery, I would like to quote those recently reported by Bailey's group, who have now done over 400 cases of mitral commissurotomy. In 214 cases which they recently reported, there were twenty-seven deaths, a mortality of 12.6 per cent. They classify the results in their cases as "excellent" in 41.6 per cent, and by "excellent" they mean "a return to normal existence without aid of drugs, except in some where the questionable need for digitalis exists." Another 32.7 per cent were "improved," and by "improved" they mean "greater activity associated with less fatigue, together with improved response to required therapy." They classify 13 per cent as "unimproved" and, as stated 12.6 per cent died.

There is no question but that, in the properly selected case, this operation offers a great deal to the patient. Some may show very striking improvement. I would like to report on one of our cases, V. H., who, prior to finger fracture of her mitral valve, had one flight dyspnea and was able to walk only one block on the level. Following operation she is able to walk an unlimited distance on the level and five flights of stairs without dyspnea of any serious degree. She has been swimming during the summer and no longer curtails any activities. Naturally, we are not always so fortunate but I do think the operation has a great future. However, the key to success is the proper selection of patients, which we will learn only with experience.

DR. TURNER: Thank you, Dr. McAllister. I would like to point out, although it is probably needless to do so, that all of this is done in an effort to combat a result of rheumatic fever. No matter how successful we may be in dealing with the effects, we should not close this clinic without re-emphasizing that our primary objective should be to understand and eradicate the cause. Without rheumatic fever there would be essentially no mitral stenosis. Unfortunately, the prevention and cure of rheumatic fever is not now possible.

DR. YALE KNEELAND: Dr. Turner, what is the evidence to show that a very slight degree of presumptive rheumatic activity is a contraindication to operation?

DR. TURNER: The experience has been that a great many of the patients who have been operated upon under such conditions, both by mitral commissurotomy and other earlier operations advised to relieve mitral stenosis, may show a marked recrudescence of rheumatic activity, with rheumatic myocarditis and death in heart failure. I believe I am correct in saying that rheumatic activity is one of the complications most feared by the surgeon.

DR. MCALLISTER: Yes.

DR. HENRY ARANOW: I know this may not be the proper place to bring this up, but one of the

questions that is frequently raised in the handling of patients with mitral stenosis who are fibrillating is whether or not it is worth while—this is quite apart from the surgical attack—to convert such patients to sinus rhythm first, since these people show a particularly great tendency toward recurrence of fibrillation. I wonder if you would comment on that.

DR. TURNER: I think that one should not waste too much effort in trying to convert auricular fibrillation to sinus rhythm in the presence of a tight mitral stenosis with a blown-up left auricle. I think you are doomed to failure in most instances.

DR. ROBERT NOBLE: Is there good evidence that the failure associated with acute arrhythmias is due to the decreased time for diastolic filling?

DR. WEST: That is a logical explanation for it but I am sure that other factors may be involved.

DR. ROBERT F. LOEB: Dr. Turner, I would like to make two comments. First, I think the advice about not operating on the very young deserves even further emphasis because I think it is fair to say that most young people with mitral disease who die in cardiac failure do not die from their mechanical valvular defect but from recrudescence of the underlying rheumatic disease and active rheumatic myocarditis. That ought to be borne in mind.

The second point of interest concerns the length of time operated patients may derive the benefits of their operation without forming adhesions again and re-establishing a tight mitral valve. I would like to know whether Dr. Hurwitt and Dr. McAllister have any information on that point.

DR. HURWITT: I think we will have to wait a little longer before being able to say. One patient has been re-explored, with a diagnosis of recurrence of mitral stenosis, when hemoptysis recurred almost a year after operation. This patient has been discussed by Dr. Lord. At reoperation no stenosis was found but rather a severe degree of regurgitation. In the patients who died several months postoperatively no material degree of stenosis was found to have reformed, but obviously the time elapsed is not sufficient.

DR. LOEB: I wonder in relation to that, Dr. Hurwitt, whether measurements of cardiac output and pulmonary hypertension in these patients, perhaps yearly or at two-year intervals, may not give us our best information as to how long the defect has been repaired?

DR. HURWITT: I am sure that is so and I think the Bellevue group is accumulating very valuable data along that line.

DR. HAMILTON SOUTHWORTH: A few patients who have had commissurotomy have had episodes of pleuritic pain and fever within a few months after their operation. I wonder if one of the speakers would care to comment on the occurrence and the possible etiology of that phenomenon.

DR. MCALLISTER: At first it was thought to be embolic but then the pain was found to recur in the same spot and it is difficult to assume an embolus always lodging in the same spot. I think it is recurrent low-grade infection for which we have no explanation. I have noticed that the lingula is the last part of the lung to be expanded, and we have had some difficulty in expanding it after it had been rendered temporarily atelectatic. I have wondered if that had any role in the etiology of the pain.

DR. TURNER: Are there any other questions or comments?

DR. HURWITT: I would like to mention the case of saddle embolus at our hospital that Dr. McAllister referred to. This was a patient operated upon by Dr. Allen Blumberg who recognized the saddle embolus promptly and removed it successfully by prompt embolectomy. This has led to routine palpation of femoral artery pulsations pre- and postoperatively in all of our cases.

SUMMARY

DR. GILBERT H. MUDGE: Mitral stenosis is one of the most common and most important results of rheumatic fever. Although a comprehensive discussion of the problem must include the cause and prevention of the underlying disease, this clinic has focused attention on the hemodynamic aspects of stenosis as a basis for considering the newer methods of surgical therapy.

The action of the valve itself has been studied by direct visualization in experimental animals. This ingenious technic has permitted accurate description of the behavior of the valve throughout the cardiac cycle. Closure of the valve consists of two components: first, a muscular contraction of the ring which greatly reduces the aperture, and second, closure of the valve leaflets. The special significance of the large aortic leaflet is discussed.

The hemodynamic sequelae of mitral stenosis are described in an attempt to correlate the functional abnormalities with important clinical features such as dyspnea, hemoptysis and arrhythmias.

Cardiac function has been studied under different conditions of exercise, heart rate and cardiac rhythm; it can be analyzed in terms of at least three major factors, the valvular deformity, changes in the pulmonary vascular bed and the myocardial reserve of both sides of the heart. The importance of the muscular component is illustrated by the hemodynamic changes resulting from digitalization and from acute myocarditis. Physiologic effects of stenosis and insufficiency are so complex that it is often difficult to correlate symptoms with function. Since the success of surgical correction eventually depends on such a correlation, it is important to continue to follow patients by precise physiologic methods.

The indications and contraindications for the surgical correction of mitral stenosis are considered, with recognition of both the tentative nature of present data as well as the benign nature of the lesion in the vast majority of patients. Rheumatic activity must be considered a major contraindication to surgery.

The technical aspects of commissurotomy are discussed in relation to the structure and function of both the normal and diseased valve leaflets. Since acute mitral insufficiency is very poorly tolerated, the modern operation for correcting stenosis has been so devised that the baffle action of the large aortic leaflet is preserved, thus producing a "selective" mitral insufficiency. Problems of pre- and postoperative management are discussed, as are the acute circulatory changes which occur during the surgical procedure. Results of commissurotomy appear promising although longer periods of follow-up are needed for final evaluation.

Clinico-pathologic Conference

Scleroderma with Congestive Heart Failure

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. L. (No. 204321), was a white married laborer, forty-nine years of age, who was admitted to the Barnes Hospital on December 13, 1951, complaining of stiffness of the skin and generalized weakness. The family and past histories were non-contributory. The patient had enjoyed excellent health until one year before admission when he noted the insidious onset of anorexia and generalized weakness. His symptoms progressed and four months later his feet became swollen and painful. At the same time he developed pain in the ankles and knees, and over these areas his skin became tight and warm. Shortly thereafter similar involvement of the upper extremities occurred. The patient consulted a physician who told him he had arthritis and prescribed "a new medicine." During the two months in which the patient received the medication there was a decrease in ankle swelling, his skin became somewhat softer and his appetite improved. Nine weeks before entry the patient noted that his hands became blue and painful when they were exposed to cold, and small ulcers appeared on the finger tips. One month later the skin over his shoulders, hands and feet got progressively tighter and thicker, and soon his face became similarly affected. There had been no dysphagia and no cardiac symptoms; and although the patient's appetite had remained good, he had lost 26 pounds in the year prior to entry. Because of the skin changes and progressive weakness, he was referred to the Barnes Hospital.

At the time of entry physical examination revealed the temperature to be 37°C., pulse 80, respirations 18 and blood pressure 120/65. The positive physical findings were confined to the skin over the face, neck, chest and extremities which was thick and firm. It was stretched so tightly over the joints that their movements were distinctly limited. There was no significant muscle tenderness and no lymph node enlargement. The heart and lungs were normal. The neurologic examination was within normal limits. There was no pitting edema.

The laboratory data were as follows: Blood count: red cells, 4,200,000; hemoglobin, 14 gm.; white cells, 6,500; differential count, normal. Urinalysis: negative. Stool: guaiac negative. Blood cardiolipin test, negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; sugar, 71 mg. per cent; total protein, 6.9 mg. per cent; albumin, 4.2 gm. per cent; globulin, 2.7 gm. per cent. Basal metabolic rate: +28 per cent. Roentgenogram of the chest: the cardiac silhouette was normal; aside from a calcified tubercle in the right lower lobe the lung fields were clear. Barium swallow: normal esophageal peristalsis was demonstrated, and there was no evidence of an intrinsic defect. Electrocardiogram: normal.

The patient was treated with 3-hydroxy,2-phenylcinchoninic acid (H.P.C.) for three weeks and exhibited some subjective and slight objective improvement. The laboratory findings remained unchanged except that the basal metabolic rate on subsequent readings was +15 per cent and +8 per cent. A skin biopsy revealed changes compatible with early scleroderma. The patient was discharged from the hospital on January 9, 1952, to be followed in the out-patient medical clinic.

Following discharge the patient continued to take H.P.C. for two months without further improvement. He then failed to return to the clinic, and was not seen again until May 10, 1952, at which time he came to the Emergency Ward because he had vomited a cupful of blood-streaked material. He also stated that three days earlier he had noted the sudden onset of dyspnea, orthopnea and a cough productive of blood-stained sputum. He denied chills, fever or chest pain. The patient was immediately readmitted to the hospital.

Physical examination revealed his temperature to be 37°C., pulse 140, respirations 40 and blood pressure 190/100. The patient appeared critically ill. He was orthopneic, tachypneic and mildly cyanotic. Examination of the skin revealed brown pigmentation over the face, hands and feet. The retinal arterioles were markedly narrowed, and hemorrhages and exudates were visualized in both fundi. The neck veins were distended. There were inspiratory moist rales over the lower portions of both lung fields. The heart was not enlarged to percussion and no murmurs were heard, but a diastolic gallop rhythm was audible. Except for 2+ pedal edema, the remainder of the physical examination was within normal limits.

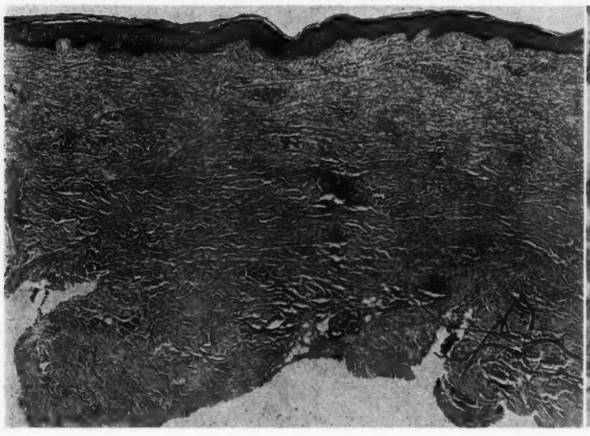
The laboratory data were as follows: Blood count: red cells, 3,500,000; hemoglobin, 9.5 gm.; white cells, 12,050; differential count: stab forms 6 per cent, segmented forms 62 per cent, lymphocytes 29 per cent, monocytes 3 per cent. Clotting time: 7½ minutes. Sedimentation rate: 28 mm. per hour. Urinalysis: specific gravity, 1.008; albumin, 2+; sugar, negative; centrifuged sediment, occasional granular casts, white cells and red cells. Stool: guaiac positive. Blood chemistry: non-protein nitrogen, 52 mg. per cent; total protein, 5.6 gm. per cent; albumin, 2.9 gm. per cent; globulin, 2.7 gm. per cent; chloride, 82 mEq./L.; CO_2 combining power, 20 mEq./L. Roentgenogram of the chest: the findings were compatible with marked pulmonary edema. The cardiac silhouette appeared within normal limits. Electrocardiogram: left ventricular strain and sinus tachycardia.

Immediately upon admission the patient was digitalized, given intravenous aminophyllin and positive pressure oxygen. Although the orthopnea was lessened, tachypnea persisted. The patient continued to cough and to bring up blood-tinged sputum; cultures of the sputum revealed no pathogenic organism. The maximum temperature recorded during the first two hospital days was 38.8°C. The temperature promptly subsided with penicillin and streptomycin therapy and remained normal thereafter. The urinary output diminished and mercurial diuretics were ineffective. By the third hospital day the patient's non-protein nitrogen had risen to 110 mg. per cent. The sodium was 131 mEq./L. and the potassium 5.3 mEq./L. A repeat electrocardiogram showed digitalis effect but was otherwise unchanged from that obtained at the time of admission. The patient was transfused with 5 units of washed red blood cells, and cortisone therapy in a dose of 200 mg. a day was begun. On the fourth hospital day the patient was somewhat improved and another chest film showed some clearing of the pulmonary edema. By the sixth hospital day, May 15, 1952, the blood non-protein nitrogen had risen to 164 mg. per cent, the chloride was 90 mEq./L., the sodium 136.7 mEq./L., the carbon dioxide combining power 21.4 mEq./L. and the potassium 8.1 mEq./L. The urinary output fell to 100 cc. During the course of the day the patient became progressively obtunded and expired suddenly.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Since there seems to be no question that this patient was suffering from scleroderma, we will have an opportunity to discuss this interesting disease. In past years scleroderma has been uncommon in the Barnes Hospital. As a matter of fact, over the past twenty-year period approximately one patient per year has been admitted with scleroderma. In 1952 a remarkable change has taken place in that in the first nine months of this year eleven new patients with scleroderma have been seen. As we are all aware, scleroderma causes not only skin lesions of a striking type but visceral lesions as well. To begin I would like to ask Dr. Weiss to discuss the dermatologic aspects of the disease.

DR. RICHARD S. WEISS: Before it was well recognized that scleroderma was a generalized systemic disease, most patients with scleroderma were seen by dermatologists, and most of the early observations are to be found in the dermatologic literature. In recent years many patients with scleroderma have been studied by internists, and considerable information has been obtained in regard to the systemic manifestations of the disease. As far as the skin lesions are concerned the first symptom which most patients with scleroderma observe is a slight tightening of the skin, often beginning over the face. Soon thereafter, the skin of the neck, anterior chest and then of the extremities, particularly of the fingers, becomes similarly involved. Years ago patients with scleroderma who were seen early in the course of the disease were frequently told they had arthritis; this misconception arose because the patients often complained of pain, stiffness and limitation of motion of the joints. Actually, of course, the joint manifestations are secondary to those affecting the skin.



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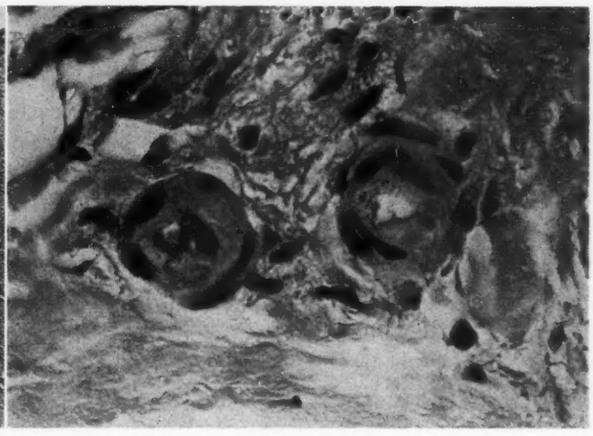

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FIG. 1. A biopsy of the skin showing atrophy of the epidermis and the thickened collagen of the dermis extending below the persistent sweat glands.

FIG. 2. Thickened arterioles in the dermis.

Similar changes occur in the skin of the face so that the patient may have difficulty in opening his mouth to the fullest extent. The nose may shrink and a characteristic pinched appearance of the face is noted. As the skin of the fingers becomes progressively involved, atrophy occurs, ultimately leading to contraction and "claw-like hands." The toes are frequently affected similarly. Because there is often associated ischemia, Raynaud's phenomenon is simulated. As the disease progresses, more and more of the skin area becomes involved, the patient becomes bedridden and almost helpless.

Scleroderma is now considered to be one of the so-called collagen diseases and reasonably so, since the collagenous tissue undergoes profound alteration, first by swelling and later by atrophy. Although the outlook for advanced scleroderma is generally poor, we have recently had a small measure of success in the treatment of a few patients with ACTH and cortisone. It may be that if treatment is instituted before profound changes have occurred in the tissues, the results may be more favorable.

DR. ALEXANDER: Thank you, Dr. Weiss. It will be recalled that this patient was subjected to a skin biopsy, and the biopsy specimen was said to have been characteristic of scleroderma. Dr. Cooper, would you comment on the biopsy findings?

DR. ZOLA K. COOPER: The section shown in Figure 1 was taken from the biopsy obtained during the patient's first admission. There is atrophy of the epidermis and almost complete obliteration of the rete pegs. The few which remain are short and blunt. The collagen bundles show homogenization and swelling. The cellular infiltration around the blood vessels is minimal. The hair follicles and sebaceous glands are no longer present, but the sweat glands persist and are surrounded by collagen. The latter finding has been interpreted by Lever[1] to indicate proliferation of collagen. Although ultimately in advanced scleroderma the sweat glands are also lost, they persist longer than any other skin appendages. Other sections from the biopsy revealed increased pigmentation in the basal layer of the epidermis.

In Figure 2 two blood vessels are shown. There is striking thickening of the vessel walls but the lumens are still patent.

DR. ALEXANDER: This patient noted that the tips of his fingers became blue and painful on exposure to the cold. Subsequently, small ulcers developed. As Dr. Weiss has mentioned, there seem to be features common to both scleroderma and Raynaud's disease. Dr. Goldman, would you discuss this relationship?

DR. MELVIN L. GOLDMAN: Raynaud's phenomenon can occur in a number of diseases of which scleroderma is one. Early in the course of scleroderma, when Raynaud's phenomenon is a not uncommon concomitant, differentiation of the former from Raynaud's disease is difficult or impossible.

DR. ALEXANDER: Dr. Weiss, would you tell us something about scleredema and discuss its relationship to scleroderma.

[1] LEVER, W. F. Histopathology of the Skin. Philadelphia, 1949. J. B. Lippincott Co.

DR. WEISS: Scleredema is an entirely different disease from scleroderma. The former is an acute process which follows infectious diseases such as tonsillitis or pharyngitis. Patients with scleredema develop edematous, thickened skin about the face, neck, chest and upper shoulders, which may resemble scleroderma, but in contrast to the latter, scleredema is a benign entity from which recovery is the rule.

DR. ALEXANDER: Let us now consider certain of the visceral manifestations of scleroderma. This man had several chest x-rays and apparently at no time were abnormalities in size or contour of the heart demonstrated. Dr. Smith, can the heart be involved in scleroderma?

DR. JOHN R. SMITH: Yes, it can. Myocardial involvement has been described by a number of observers. There is evidence that the myocardial involvement consists of multiple areas of swelling and thickening of the collagen. Often mononuclear cellular infiltration occurs, although it may be very scant. The myocardium may be affected by bands from the epicardium to the endocardium, with destruction of varying amounts of muscle tissue. The coronary arteries are uninvolved.

DR. ALEXANDER: Does heart failure occur in scleroderma of the heart?

DR. SMITH: Yes, it does. Dyspnea is a common complaint in scleroderma heart disease. For example, all of the nine patients described by Weiss et al.[2] in their classical article on this entity had dyspnea. Peripheral edema, pulmonary congestion and other signs of congestive heart failure are not at all uncommon. In general, the patients do not respond well to the usual measures directed toward the treatment of cardiac failure.

DR. ALEXANDER: During the patient's hospital stay he was given a barium swallow, but no evidence of intrinsic disease of the esophagus was demonstrated. Dr. Mendeloff, how often does scleroderma affect the esophagus?

DR. ALBERT I. MENDELOFF: The esophagus is one of the more common sites of visceral scleroderma. The stomach is rarely involved but the small intestine may be, and it is probable that scleroderma of the colon may also occur. It is difficult to be certain in what per cent of patients with scleroderma the esophagus is affected, but the figure may be of the order of 30 to 35 per cent. Commonly the lower third of the esophagus is the site of pathologic change, and there are usually lesions in the smooth musculature similar to those in the myocardium. In the advanced stage the muscle is destroyed and fibrosis develops. The esophagus loses its normal primary and secondary peristalic activity, becomes stiff and tends to remain open at all times. The findings on endoscopic examination are quite typical. In some instances there may be narrowing of the lower third resulting in stricture. The dysphagia of which patients with esophageal scleroderma complain may be indistinguishable from that described by patients who have organic strictures from tumors, achalasia or cardiospasm. Superimposed, there is frequent peptic esophagitis.

When the small bowel is involved the loops are often dilated and paralytic ileus may develop. On the other hand, we have seen one patient who had thirty to forty stools daily, apparently due to a complete loss of tone in the small bowel. Thus there was very little resistance to the flow of intestinal contents. The patient developed severe hypokalemia and expired.

DR. ALEXANDER: Dr. Elliott, would you comment on the radiologic findings in scleroderma of the gastrointestinal tract?

DR. GLADDON V. ELLIOTT: When the esophagus is involved in scleroderma, the radiologic abnormalities which are most striking are those due to stricture in the distal third. It is of interest that when stricture develops in scleroderma it usually occurs at a point 4 to 5 cm. above the diaphragm, a site which permits its radiologic differentiation from strictures due to cardiospasm or peptic esophagitis *per se*. The involved area may be only 2 to 3 cm. in length. If one suspects esophageal scleroderma, fluoroscopic examination is apt to be most helpful, particularly if it is done with the patient in a horizontal position so that the examiner may observe any decrease or absence of peristalic activity inferior to the suprasternal notch. The character of the esophageal mucosa in sclerodermal disease has been commented upon by various radiologists. In general, the mucosal folds tend to be rather broad and coarse in contrast to the fine parallel folds seen in the normal esophagus. We have recently been reviewing the cases of scleroderma in which x-ray examinations have been made. It is our impression that abnormalities in the esophagus have been demonstrated in about 50 per cent of the patients. To date we have

[2] WEISS, S., STEAD, E. A., JR., WARREN, J. V. and BAILEY, O. T. Scleroderma heart disease. *Arch. Int. Med.*, 71: 749, 1943.

demonstrated no lesions in the stomach which we can consider related to scleroderma. The changes in the small intestine are rather nonspecific, and we are unwilling to make a diagnosis of small intestinal scleroderma on the basis of radiologic examination.

DR. ALEXANDER: Thank you, Dr. Elliott. As is obvious, there is much to suggest that scleroderma may involve a number of organs and recently attention has again been directed to the possible relationship of scleroderma and endocrine abnormalities. Dr. Daughaday, would you discuss this point?

DR. WILLIAM H. DAUGHADAY: There has been a large amount written in the literature over the past years concerning the question of endocrine involvement in scleroderma. About fifteen to twenty years ago it was fashionable to ascribe an endocrine cause to any undiagnosed disease. I do not believe that there is significant evidence relating thyroid, parathyroid or adrenal abnormalities to the pathogenesis of scleroderma, although at different times all three glands have been implicated. For example, it was thought that hypothyroidism might be a factor, a concept which probably arose because, in a very superficial fashion, some of the skin changes in scleroderma seemed similar to those of myxedema. Likewise, by virtue of the fact that sclerodermal plaques sometimes become calcified, it was suggested that the parathyroids were involved and parathyroidectomy actually was performed in a few patients with scleroderma.

In regard to the role of adrenal dysfunction in scleroderma, the evidence does not support the hypothesis that the adrenal is primarily responsible. It is probable that adrenocortical function may be secondarily depressed in scleroderma, but whether the pigmentation and weight loss are related to adrenal involvement or not is conjectural. The 17-ketosteroid excretion has been measured in patients with scleroderma and has been found to be decreased in some. Similarly, changes in the glucose tolerance curve, consistent with adrenal insufficiency, have been reported. The problem involved is one which is common to a number of chronic diseases in which some abnormalities in adrenal function can be demonstrated, but in which there is great likelihood that the changes are effect rather than cause. It should also be emphasized that the fact patients with scleroderma may exhibit improvement after cortisone therapy does not speak in favor of adrenal insufficiency being responsible for the original disease. One need only consider the beneficial effect of cortisone in rheumatoid arthritis, a disease in which primary adrenal insufficiency cannot be demonstrated.

DR. ALEXANDER: One of the very interesting problems presented by this patient was the rapid appearance of the signs of cardiac failure. The patient was in reasonably good condition when he left the hospital the first time, but within four months he reappeared with hypertension, oliguria and azotemia. Dr. Schroeder, would you comment on this chain of events?

DR. HENRY A. SCHROEDER: The most obvious explanation would be that the blood vessels of the kidneys were the site of pathologic changes comparable to those involving the vessels of the skin, heart and esophagus, thus leading to progressive renal impairment. In other words, I would predict that the patient's kidneys will show lesions which are typical of those found in the so-called collagen diseases. Possibly the "wire-loop" lesions of disseminated lupus or the changes characteristic of polyarteritis nodosa will be demonstrated. In patients succumbing to one of the collagen diseases it may be difficult for the pathologist to make a clear-cut differentiation always; in other words, there may be some "overlap."

DR. ALEXANDER: Would you say something about the oliguria?

DR. SCHROEDER: It probably resulted from the rapidly advancing renal insufficiency. It is also possible that the mercurial diuretic which the patient was given was detrimental, since mercurials can have adverse effects in patients with azotemia. Further, mercurial diuretics are particularly ineffective in the presence of the low salt syndrome which this patient had to some degree.

DR. ALEXANDER: What role, if any, did the cortisone play in renal failure?

DR. SCHROEDER: Cortisone may have resulted in salt retention, and may have had an unfavorable effect in this regard.

DR. ALEXANDER: It might be proper to ask Dr. Germuth about the incidence of kidney involvement in scleroderma.

DR. FREDERICK G. GERMUTH: I will discuss that point in more detail when I present the pathologic findings, but in four cases which I have collected recently two had some renal involvement.

DR. ALEXANDER: Dr. Shapleigh, would you say a word about the use of H.P.C.?

DR. JOHN B. SHAPLEIGH: In 1950 Blanchard et al.[3] showed that H.P.C. produced a fall in adrenal ascorbic acid in rats similar to that seen after ACTH administration. This observation suggested that the drug might be of value in those diseases in which ACTH was beneficial. When it was given to several patients with rheumatic fever[4] it had a favorable response in terms of fall in temperature and relief of joint pain, although some relapses occurred when the drug was stopped. Subsequently, H.P.C. was used for other collagen diseases, including disseminated lupus erythematosus, scleroderma and polyarteritis nodosa. The most striking results obtained were in three patients with scleroderma who received the drug for periods ranging from seven to twenty-one days. All three improved either during or shortly after therapy. Two of the three patients relapsed after therapy was discontinued, but the third one did well for a significant period of time.

DR. ALEXANDER: The final point which I should like to bring up for discussion concerns the chest x-ray findings. Dr. Elliott, would you comment on them?

DR. ELLIOTT: The first chest film taken during the terminal phase of the patient's illness showed a diffuse infiltration extending outward from both hilar areas in a fan-shaped or butterfly wing distribution. We have come to associate such a radiologic picture with several entities, among them being so-called azotemic pneumonia. The infiltration is attributed by some radiologists to pulmonary edema, although its appearance differs from that usually seen in classical pulmonary edema. Sante recently has called attention to the association of similar pulmonary infiltration with certain of the collagen diseases, and has suggested the term "antigenic pneumonitis." In our experience comparable findings are not infrequent in polyarteritis nodosa particularly. We have neither seen them nor have they been described in scleroderma. I therefore suspect the pulmonary changes in this case were due to azotemia rather than to scleroderma. A repeat film, made four days after the original one, showed some evidence of clearing coincident with the temporary clinical improvement made by the patient.

DR. ALEXANDER: Do you have any additional comments, Dr. Goldman?

DR. ALFRED GOLDMAN: I would agree with Dr. Elliott's interpretation, namely, that the radiologic findings were probably due to the azotemia rather than to scleroderma.

DR. ALEXANDER: Recently it has been suggested that scleroderma could be a manifestation of hypersensitiveness, perhaps to penicillin, just as polyarteritis nodosa has been associated with sulfonamide toxicity. This postulation is based on the apparent increase in the incidence of scleroderma, but the situation cannot be clarified until much additional evidence has been accumulated. Are there any additional suggestions or comments?

DR. MELVIN L. GOLDMAN: In regard to therapy, Dr. Alexander, I would like to mention that we have recently treated a patient with generalized scleroderma with hexamethonium. The results were rather impressive in that the skin lesions on the chest disappeared.

DR. ALEXANDER: I assume you were directing therapy against the vascular involvement.

DR. GOLDMAN: Yes, that is correct.

DR. ALEXANDER: In summary, I think we would all agree that this patient had scleroderma, and died of congestive cardiac failure and renal insufficiency, possibly secondary to scleroderma.

Clinical Diagnoses: Scleroderma; cardiac and renal insufficiency; ? secondary to scleroderma.

PATHOLOGIC DISCUSSION

DR. GERMUTH: Primarily as a result of the pathologic investigations of Klemperer and others a group of diseases which have in common certain basic alterations in the connective tissue have been designated as so-called collagen diseases. Both the collagen and the ground substance are particularly affected in these diseases, which include polyarteritis nodosa, rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus and scleroderma. The changes which the connective tissues undergo in these diseases are both destructive and proliferative, and inflammation may or may not be present. The pathologic

[3] BLANCHARD, K. C., DEARBORN, E. H., MAREN, T. H. and MARSHALL, E. K., JR. Stimulation of the anterior pituitary by certain cinchoninic acid derivatives. *Bull. Johns Hopkins Hosp.*, 86: 83, 1950.

[4] BLANCHARD, K. C., HARVEY, A. M., HOWARD, J. E., KATTUS, A., MARSHALL, E. K., JR., NEWMAN, E. V. and ZUBROD, C. G. The effect of 3-hydroxy-2-phenylcinchoninic acid upon rheumatic fever. *Bull. Johns Hopkins Hosp.*, 87: 50, 1950.

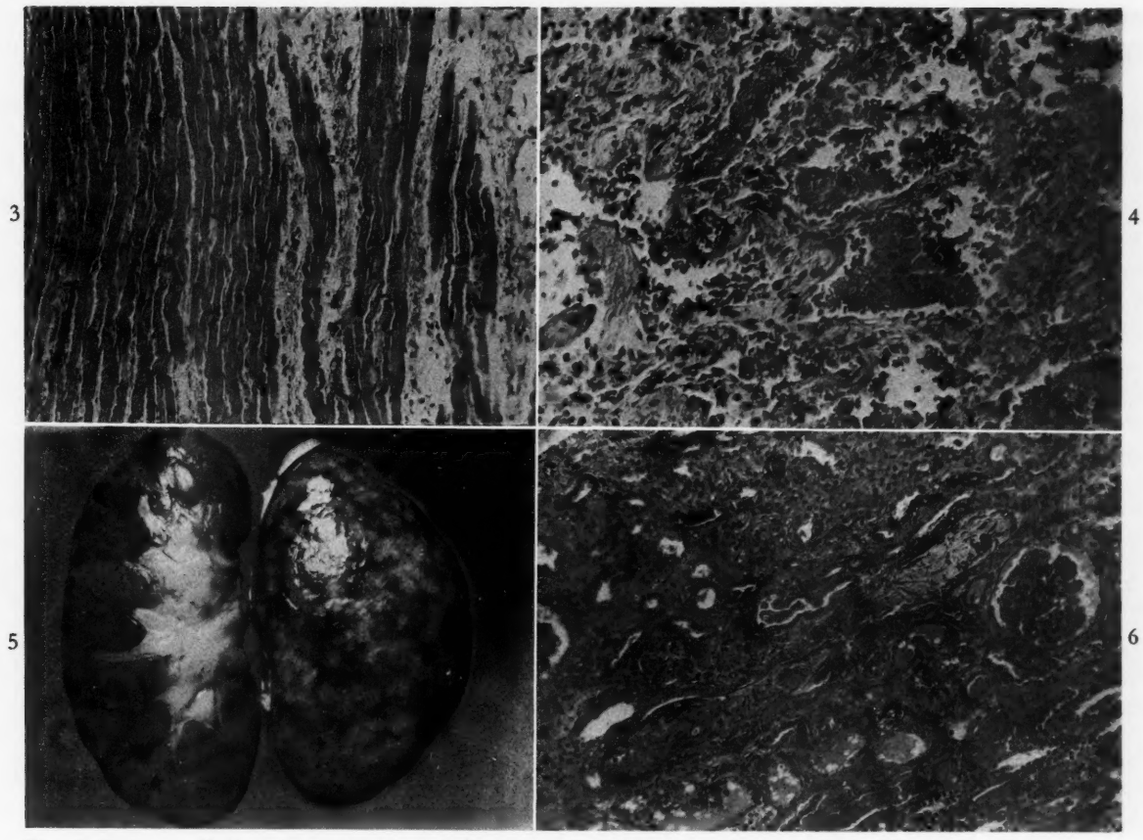

FIG. 3. Loose acellular connective tissue between myocardial fibers in scleroderma. The degree of coronary arteriosclerosis was slight and this fibrosis did not have the density or perivascular distribution of the usual interstitial fibrosis of the heart.

FIG. 4. Interstitial fibrosis and intra-alveolar fibrin in the lung.

FIG. 5. Capsular and cut surface of the kidneys showing the patchy hemorrhages in the outer half of the pale, yellow cortex.

FIG. 6. Proliferated fibrous intimal connective tissue of a loose, acellular type in an intralobular artery in the kidney.

findings differ in the degree and sites of the various basic changes. Scleroderma is usually characterized by the absence of marked destructive changes such as fibrinoid alteration and by the absence of an inflammatory reaction. Fibroblastic proliferation usually dominates the microscopic picture. The present case is of interest in that in addition to collagenous overgrowth in the skin, the heart and the lungs, there was widespread fibrinoid alteration of small arteries and arterioles of the heart, pancreas, adrenals and kidneys. In the pancreas and kidneys, probably as a consequence of the vascular inflammation, there were numerous foci of recent necrosis.

The heart was moderately enlarged to a weight of 450 gm. and had a thin, irregular deposit of fibrin over the epicardium. Microscopically (Fig. 3) numerous foci were observed of atrophic muscle fibers surrounded by loose, acellular connective tissue. In some places fat cells were present in the connective tissue; in others, the connective tissue contained numerous capillaries filled with blood. Changes in the small blood vessels were of two types: fibrous thickening of the small arteries and arterioles, and occasional deposition of Schiff-positive fibrinoid material beneath the endothelium of a small artery. It is noteworthy that only a very slight degree of arteriosclerosis was present in the coronary arteries. The lungs showed a rather marked degree of interstitial fibrosis. (Fig. 4.) This finding was more prominent in some areas than in others. Many alveoli contained clumps of fibrin and blood compatible with a recent episode of congestive failure.

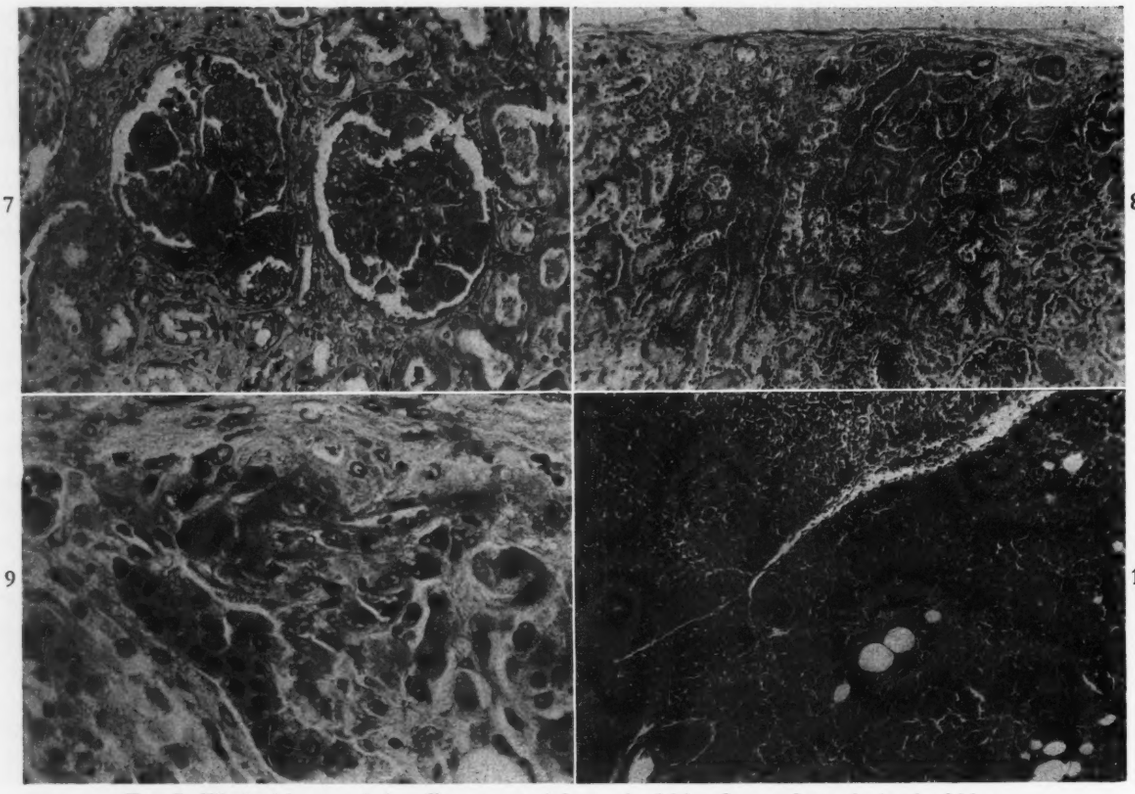

FIG. 7. Fibrinoid necrosis in afferent arterioles and within glomerular tufts in the kidney.

FIG. 8. An area of recent infarction with interstitial hemorrhage in the outer cortex.

FIG. 9. Fibrinoid necrosis in an arteriole in the zona glomerulosa of the adrenal.

FIG. 10. A focus of recent necrosis in the pancreas.

The kidneys, which weighed 150 and 180 gm., respectively, showed remarkable gross and histologic appearances. (Fig. 5.) The pale yellow surfaces were slightly uneven, and were mottled with very red foci which were obviously sites of hemorrhage. On the cut surface the thickness of the cortex was about normal, and the red foci seen on the surface were more or less confined to the outer one-half of the cortex. The medulla was normal. Histologically, it was apparent that the primary site of damage in the kidney was in the small arteries and arterioles. These showed similar but more extensive changes than the vessels observed in other organs. As illustrated in Figure 6, the intralobular arteries showed a striking proliferation of loose, acellular connective tissue beneath the endothelium. In the literature this appearance has been described as resembling Wharton's jelly. Beneath the intima of some of these vessels there were small deposits of pink-staining homogeneous material with the appearance of fibrinoid. Some of the vessels were occluded by recent and organizing thrombi. In addition to these alterations in the intralobular arteries, numerous afferent arterioles showed fibrinoid necrosis of the intima and media. As in the region shown in Figure 7, the fibrinoid in the arterioles was sometimes continuous with deposits of similar material in the loops of the glomerular tufts. The cortex also contained numerous small areas of necrosis or infarction (Fig. 8) which probably varied in age from a few hours to several weeks. Some of these areas were bordered by hemorrhage, others were surrounded by leukocytes and in some there was beginning fibroblastic invasion. The microscopic picture of the medulla was normal.

The small arteries and arterioles of the pancreas and adrenals showed fibrinoid change. In the adrenals this change was observed in the small vessels of the zona glomerulosa, as shown in Figure 9, but not in the arteries in the capsule or the periadrenal fat. In the pancreas (Fig. 10) there were numerous microscopic areas of recent necrosis in association with vascular

involvement of the same types seen in other organs.

It might be mentioned that aside from the lesions directly related to scleroderma, there were changes both in the liver and esophagus. The liver was congested and there was slight centrilobular necrosis, probably the result of the anoxemia related to cardiac and pulmonary dysfunction. The mucosa of the esophagus was eroded and there was an extensive accumulation of fibrin in the submucosa. No fibrosis was observed in this or any other portion of the gastrointestinal tract.

In summary, this was a case of scleroderma with marked involvement of the viscera, including the heart, lungs, pancreas, adrenals and kidneys. The extensive involvement of the kidney leading clinically to the rapid development of uremia was similar to what has been described recently by Moore and Sheehan.[5] These workers described three cases of scleroderma in which the cause of death was renal failure. They pointed out that the renal lesions in scleroderma, although inconstant, are unlike those in any of the other collagen diseases and are specific for this condition. They are certainly unusual lesions in human pathology; however, they resemble in a striking degree the bilateral cortical necrosis of the kidneys of rabbits resulting from the generalized Shwartzman reaction recently described by Thomas and Good.[6] Whether there is any significance in this resemblance, I don't think we can say at the present time.

Final Anatomic Diagnoses: General scleroderma; interstitial fibrosis in the heart and lungs; fibrinoid alteration in small arteries and arterioles in the kidneys, heart, pancreas and adrenals; focal necrosis in the cortex of the kidney and in the pancreas; ulcerative esophagitis.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[5] Moore, H. C. and Sheehan, H. L. The kidney of scleroderma. *The Lancet*, 1: 68, 1952.

[6] Thomas, L. and Good, R. A. Generalized Shwartzman reaction. *J. Exper. Med.*, 95: 409, 1952.

Case Reports

Deep Thrombophlebitis and Pulmonary Embolism in Thromboangiitis Obliterans

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THE pathologic anatomy and physiology of thromboangiitis obliterans involves both the arterial and venous circulations chiefly of the extremities. However, in the usual clinical course of the disease so completely do the manifestations of disturbance of the arterial blood supply of the extremities dominate the clinical picture that scant reference has been made to the manifestations of venous disease by authors on thromboangiitis obliterans. Generally the discussion of venous disease is limited, and leaves one with the impression that a recurrent superficial phlebitis occurs which may be of considerable aid in the arrival at a correct diagnosis, as well as a problem therapeutically. The deep thrombophlebitis and its complications are discussed briefly if at all.

Homans,[1] in his monograph on circulatory disease of the extremities, states without qualification that in thromboangiitis obliterans it is only the arterial disease which is of consequence. He discusses superficial migratory phlebitis but omits any mention of deep thrombophlebitis and pulmonary embolism.

The text on peripheral vascular disease by Allen, Barker, and Hines[2] contains a rather detailed description of the superficial phlebitis of Buerger's disease. In regard to the deep veins they state that phlebitis of the anterior and posterior tibial veins is an early and common manifestation but that only rarely is it clinically evident. Iliofemoral and axillary phlebitis, they note, almost never occurs. Pulmonary embolism with infarction has in their experience been known to occur, and they believe it to be rarely fatal. They suggest by inference that the cause of the relative infrequency and benignancy of pulmonary embolism in phlebitis of thromboangiitis is the predominantly endothelial and proliferative nature of the process as contrasted to, for instance, the predominantly phlebothrombotic character of postoperative phlebitis.

Kahn,[3] in a series of 164 cases of thromboangiitis obliterans encountered in an army hospital during World War II, found two cases in which a deep thrombophlebitis was the most prominent clinical manifestation at one stage of the disease. Each of these two patients was admitted to the hospital because of an iliofemoral phlebitis which overshadowed the symptoms due to the arterial disorder. In his Case 1 the iliofemoral phlebitis was bilateral and the patient suffered a pulmonary embolus with infarction of the right lower lobe of the lung. A bilateral femoral vein ligation was done in spite of almost complete occlusion of the right popliteal, dorsalis pedis and posterior tibial arteries and similar involvement of the left dorsalis pedis and posterior tibial arteries. There was apparently no very obvious change in the nutrition of the limbs following the venous ligations although persistent massive edema necessitated the wearing of elastic leg supports.

Edwards[4] states that in phlebitis of thromboangiitis obliterans the superficial veins are always affected and that it is uncertain how often the deep veins are. He also notes that iliofemoral phlebitis is extremely infrequent and that pulmonary embolism, except as a complication of iliofemoral phlebitis, is rare. He observes that he knows of one case of fatal and one case of non-fatal pulmonary embolism in Buerger's disease each from an obvious process in the femoral vein.

During the past year I encountered in a period of four months three patients with thromboangiitis obliterans in whom at the time the symptoms of deep venous involvement and pulmonary embolism greatly overshadowed those of the obstructive arterial disease. Proceeding with the investigation of these patients under the impression that this state in Buerger's disease was exceedingly rare, and handicapped by the absence of reports in the literature of

experience in the treatment of deep thrombophlebitis with pulmonary embolic episodes, such a number of diagnostic and therapeutic problems arose that the cases appeared well worth presenting, particularly since in each instance a different therapeutic approach was chosen.

CASE REPORTS

CASE I. D. A., a fifty-two year old, white gentile railroad man, was admitted to the hospital on February 27, 1951. He had apparently been well until January 20, 1951, when a pleuritic type of left lower chest pain, dyspnea and cough, and hemoptysis suddenly developed. These symptoms were of about five days' duration following which the patient felt quite well again. Three weeks later he had recurrence of the same symptoms with, in addition, pain over the left shoulder region. Because of persistence of these symptoms he visited the railroad dispensary and was then admitted to the hospital. He had no complaints referable to impairment of the arterial circulation of the extremities.

In the hospital the patient stated that twenty years previously he had suffered a traumatic amputation of the right great toe. One year ago he had been hospitalized because of an idiopathic left iliofemoral thrombophlebitis manifested by systemic temperature elevation and by pain and swelling of the entire left lower extremity. Since this episode he had noted mild swelling of the left leg when he was up and about.

Physical examination revealed abnormalities only of the lower extremities. There was no evidence of active deep or superficial phlebitis.

Artery	Pulsation	
	Right*	Left
Femoral	4	4
Popliteal	2	2
Dorsalis pedis	0	1–2
Posterior tibial	0	0

* Arterial pulsations graded 0 to 4 in which grading 0 signifies absence of the pulsation and 4, a normal pulsation.

There was fullness of the superficial veins of the left leg. Pallor occurred upon elevation: right foot grade III,* left foot grade II; rubor was seen upon dependency: right foot grade II, left foot grade 0-I. Venous filling was delayed bilaterally and absence of the right great toe was noted.

FIG. 1.

X-ray of the chest (Fig. 1) revealed a left diaphragmatic adhesion with tenting of the diaphragm. There was a faint increase in density opposite the second left interspace suggesting an infiltrating lesion. At the level of the fifth and sixth interspace on the left there was a wedge shaped area of increased density suggestive of pulmonary infarction.

In the absence of any clinical signs of phlebitis and because of the rarity of pulmonary embolism in the phlebitis of Buerger's disease, an investigation of the respiratory system was believed necessary. Examination of the sputa for malignant cells and for tubercle bacilli were negative as was bronchoscopic and bronchographic examination of the tracheobronchial tree.

The patient made an uneventful recovery from the pulmonary infarction without any treatment. He was advised to stop smoking, was instructed in the usual protective measures in regard to the feet and was placed on vasodilators

* Pallor and rubor graded I to IV in which grading I indicates the least and IV, the most severe degree of the abnormality.

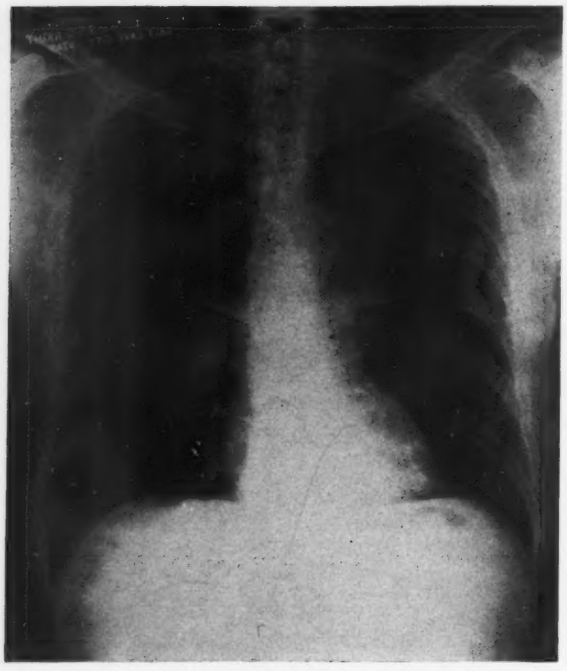


FIG. 2.

including alcohol and priscoline. Following discharge from the hospital on March 10, 1951, the patient returned to his usual occupation and at this time became increasingly aware of intermittent claudication of both calves. He was started on injections of pancreatic tissue extract without noticeable improvement. He complained of increasing exertional dyspnea but there was nothing to suggest additional pulmonary thromboembolic episodes. X-ray of the chest (Fig. 2) on April 18, 1951, showed no evidence of recent infarction and resolution of the previous changes, which now appeared more definitely to have been embolic in origin.

On April 28, 1951, an acute superficial phlebitis of the dorsum of the left foot developed which was painful and incapacitating enough to necessitate the patient's admittance to the hospital. Intravenous typhoid vaccine was administered on alternate days with satisfactory chills and fever occurring from April 29th to June 4th. In spite of this and continuous prolongation of the prothrombin time to 35 seconds or above the superficial phlebitis continued to migrate and to involve additional veins of the left foot and leg. On May 15, 1951, an iliofemoral phlebitis of the left lower extremity developed, with marked swelling up to the inguinal region. In the succeeding weeks the edema and migratory superficial and deep phlebitis gradually subsided and by June 11, 1951, no evidence of acute phlebitis had been apparent for one week. Moderate swelling of the left ankle and leg was noted as the patient was up and about.

At this time, because of the recent evidence of bilateral progressive impairment of the arterial circulation of the extremities and the deep thrombophlebitis with multiple pulmonary embolic episodes and pulmonary infarction, it was concluded that the treatment of choice would be a transabdominal bilateral lumbar sympathectomy and inferior vena caval ligation. These procedures were carried out on June 19, 1951. Postoperatively the patient developed on the right an obvious severe phlebitis of the superficial veins and apparently also of the anastomotic deep veins with pain and swelling of the entire right lower extremity. The acute phlebitis gradually subsided and the patient was dismissed on July 3, 1951, at which time he had edema much more pronounced on the right than on the left. The edema was moderately well controlled by elastic stockings.

On July 13, 1951, the patient was readmitted to the hospital for a two week's course of intravenous typhoid vaccine therapy because of recurrence of the superficial phlebitis on the right. When last seen in December, 1951, the patient was able to work at his usual occupation although with some difficulty because of the persistent massive edema of the lower extremities, which extended peripherally from the inguinal region bilaterally. The edema was controllable with heavy elastic supports to the knee, but because of the chafing and discomfort of the heavy supports the patient preferred to allow considerable edema to occur while wearing lighter elastic stockings. The intermittent claudication had become much less troublesome, appearing after walking four long city blocks rather than one as previously. Exertional dyspnea caused greater incapacitation than the symptoms referable to the extremities. The patient had ceased smoking completely.

CASE II. R. P., a forty-eight year old white gentile male stockbroker whose history dated back to August, 1947, at which time he had suffered a deep thrombophlebitis of the right lower extremity manifested by systemic temperature elevation and pain and swelling of the right lower extremity. Heat and elevation as well as dicumarol had been employed in the treatment and recovery had been uneventful. No diminution of the arterial pulsations was apparent at

that time. In the subsequent years intermittent claudication of both calves developed and in February, 1951, the patient suffered an acute arterial occlusion of the right lower extremity. Although the impending gangrene of the right foot responded to protection, papaverine, mild heat and repeated right lumbar parasympathetic novacain block, it had been thought advisable to do a right lumbar sympathectomy which was carried out on February 6, 1951. Following this procedure there was a rise of the skin temperature of the right calf; however, the right foot remained considerably cooler than the left.

After hospital discharge the patient continued to suffer considerably from pain and paresthesias of the right foot and leg, complaining of numbness, crawling and tingling of the foot, and a boring and penetrating pain of the foot and calf. He was unable to walk because of the pain which was particularly severe at night and to such a degree as to prevent sleep.

The patient was readmitted to the hospital on March 20, 1951, because of the aforementioned symptoms. Examination, except for that of the lower extremities, was negative. Abnormal findings of the lower extremities were as follows:

Artery	Pulsation	
	Right	Left
Femoral	4	4
Popliteal	0	2–3
Dorsalis pedis	0	2
Posterior tibial	0	2

Pallor occurred upon elevation: right foot grade III, left foot grade I; rubor was seen upon dependency: right foot grade II, left foot normal. Venous filling was normal bilaterally. The right lower extremity showed no sweating, the right foot was cool and there was a small fissure between the third and fourth right toes.

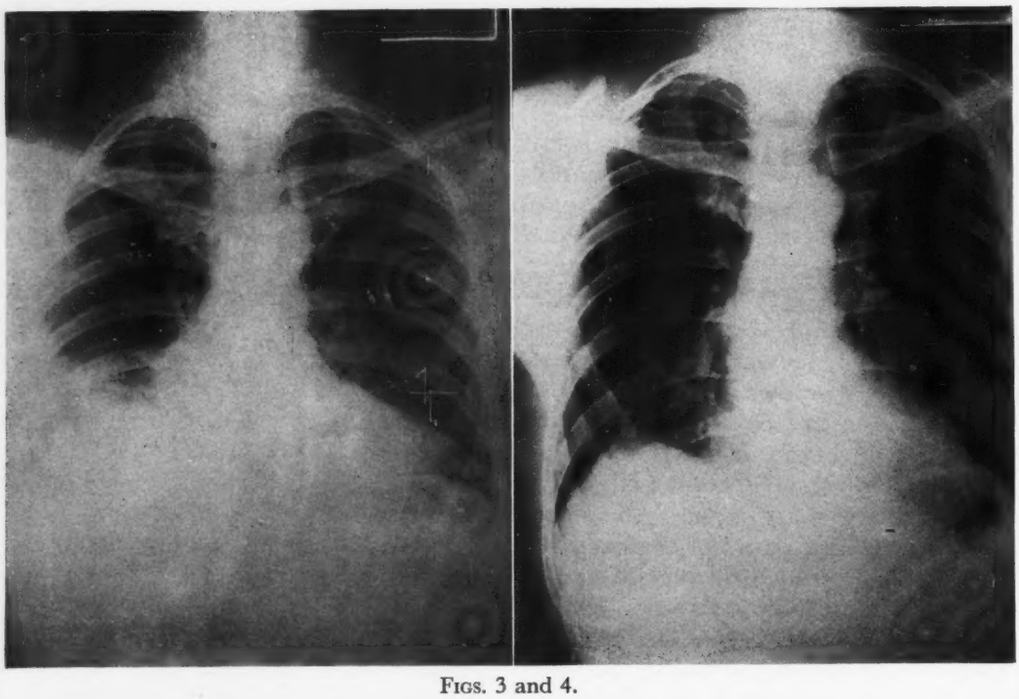
Routine laboratory studies of the blood and urine including a fasting blood sugar and blood cholesterol and cholesterol ester determinations were negative or within normal limits.

The patient was treated with bed rest, a Buerger box, alcohol, priscoline, thiamine, aspirin, and with boric soaks to the right foot. The patient was advised to and did stop smoking cigarettes completely. On alternate days he was given intravenous injections of typhoid vaccine and diathermy to the trunk. Over a period of four weeks there was considerable improvement of the arterial circulation of the right foot as manifested by healing of the fissure between the right third and fourth toes, complete disappearance of pain and paresthesia except for slight numbness of the right second and third toes, and general improvement of the appearance of the right foot. During the last week of his hospital stay he complained of some pain in the left popliteal space, the cause of which could not be ascertained.

Following discharge from the hospital on April 16, 1951, the patient continued to complain of pain in the left popliteal region, the cause of which could not at first be found. He was able to be up and about with but little discomfort except for the left popliteal pain. About two weeks after his discharge a frank superficial and iliofemoral phlebitis of the left lower extremity became apparent with pain throughout the whole extremity, marked swelling of both the left thigh and leg and numerous red, tender thrombosed superficial veins. The patient was advised to remain in bed at home since he was unwilling to re-enter the hospital. Over a period of two weeks the evidence of active phlebitis subsided although there was persistent swelling of the left leg and thigh when the patient was up and about.

He returned to his occupation and suffered little discomfort except for the edema of the left lower extremity until July 10, 1951, when a pleuritic type of pain in the lower right chest and a temperature elevation to 102°F. rather suddenly developed. He consulted his physician one week later because of persistence of the pain and was admitted to the hospital on July 17, 1951. At this time there was no obvious evidence of active superficial or deep thrombophlebitis. A friction rub and rales were audible over the right lung base posteriorly. X-ray of the chest (Fig. 3) revealed a density of the lower half of the right lung below the lesser fissure which had the appearance of a pulmonary infarction. The prothrombin time was elevated satisfactorily with dicumarol and after disappearance of the symptoms the patient was dismissed on July 26, 1951.

On September 2, 1951, the patient had another episode of pleuritic type of left lower



FIGS. 3 and 4.

chest pain of rather sudden onset associated with a dry cough and rather marked dyspnea. He consulted his physician nine days later because of persistence of the symptoms. Examination of the extremities revealed no evidence of active thrombophlebitis. Rales were audible at the left base anteriorly. X-ray of the chest (Fig. 4) showed further resolution of the right pulmonary infarction. The left lung was clear, but there was an increase in the size of the left pulmonary artery which was now two times as large on the chest x-ray two months previously. The possibility of pulmonary artery thrombosis was suggested. An electrocardiographic tracing revealed an acute right ventricular strain pattern.

Because of the recurrent pulmonary embolization at a time when any evidence of active phlebitis was absent it was believed advisable to maintain a decreased coagulability of the blood for an indefinite period in the hope that during this time the phlebitic process would become quiescent and no further embolization would occur. Dicumarol rather than heparin was chosen as the anticoagulant agent because of the greater ease of administration, the lesser cost and the patient's preference. To the present, with the patient ambulatory, the prothrombin time has been satisfactorily maintained in the region of 35 seconds without much difficulty after an initial period in the hospital to determine roughly the dicumarol tolerance. There has been no evidence of phlebitis and no further pulmonary embolic episodes to date. The patient has remained ambulatory and complains only of slight swelling, which is diminishing in degree, of the left lower extremity when up and about.

Case III. B. D., a fifty-seven year old white gentile male railroad superintendent whose history dated back to 1944 when at the age of fifty years, while in the army in France, he noted sensitivity of the feet to cold and intermittent claudication of the calves. In an army hospital in 1944 he was treated with physiotherapeutic measures with considerable relief of his symptoms. He then had only minor symptoms of impaired circulation of the lower extremities until 1947 when a progressive and rather rapid increase in the severity of intermittent claudication occurred. At this time occlusive arterial disease of both lower extremities was noted, and the patient was referred to a large midwestern clinic where a diagnosis of arteriosclerosis obliterans was made. The patient was instructed in the usual protective measures for the feet and advised to stop smoking, which he did for one year. He returned to his occupation and except for intermittent claudication of both calves after walking two city blocks felt quite well.

In April, 1951, he suffered an attack of left lower chest pain of sudden onset, associated with fever and cough. A diagnosis of atypical pneumonia was made and the patient apparently responded to treatment with penicillin in the home, becoming free of symptoms in two weeks. On May 29, 1951, approximately one month later he had what was thought to be a recurrence of the pneumonia and was admitted to the hospital on May 31st for treatment.

Upon admittance to the hospital the patient was noted to be moderately obese and acutely ill. Temperature was 102°F. Rales were audible over the left base posteriorly with evidences of pulmonary consolidation being present. Examination of the extremities revealed the following:

Artery	Pulsation	
	Right	Left
Femoral	2	2
Popliteal	0	0
Dorsalis pedis	0	0
Posterior tibial	0	0

There was no evidence of active phlebitis of either leg. Pallor of the feet occurred upon elevation: right grade II, left grade II. Rubor of the feet was seen upon dependency: right grade I, left grade I. Venous filling: right 25 seconds, left 20 seconds.

X-ray of the chest (Fig. 5) revealed a density of somewhat triangular outline in the left base adjacent to the heart shadow suggestive of, among other things, pulmonary infarct.

Although the history of occlusive peripheral vascular disease was obtained and the abnormal arterial pulsations noted, the possibility of the pulmonary disorder being on a thromboembolic basis was not considered for the following reasons: the vascular disease appeared almost surely to be arteriosclerotic in nature; there was no evidence or history of active or past phlebitis; and the rarity of occurrence of pulmonary embolic phenomena in Buerger's disease.

An investigation of the respiratory tract including examination of the sputa for bacteria, acid-fast bacilli and malignant cells, and bronchoscopy revealed nothing of diagnostic

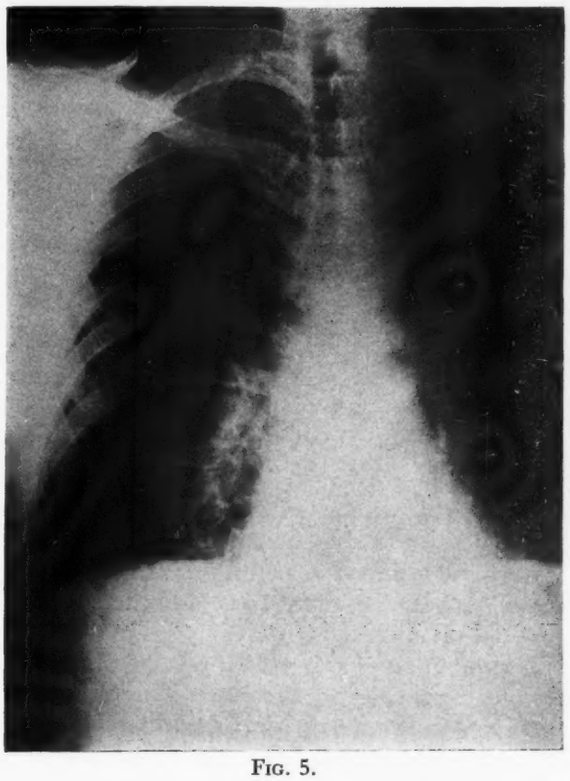


FIG. 5.

significance. The patient was treated with penicillin and dismissed on June 7, 1951.

He had recurrences of essentially the same clinical picture on June 17, 1951, and July 11, 1951, with the exception that the pain and findings were located in the right lower chest in the second episode. Chest x-rays in June showed no additional findings as compared to the previous film but in July (Fig. 6) revealed a triangular area of density projecting from the lateral wall of the left chest toward the hilus and suggestive of an infarct. The patient was hospitalized with each recurrence and aside from his usual complaints as to claudication had no symptoms or findings to suggest thrombophlebitis or activity of the occlusive arterial disease. During the third hospitalization because of a complaint of mild dysphagia the esophagus was examined radiographically with barium and an esophageal hiatus hernia was found. The possibility that the pulmonary disorder was due to aspiration pneumonitis was considered. Symptoms due to the hiatus hernia were completely relieved by symptomatic measures and a 30 pound weight loss.

On August 11, 1951, severe crampy pain of the left foot developed and within twelve hours the left calf was also involved. The pain was

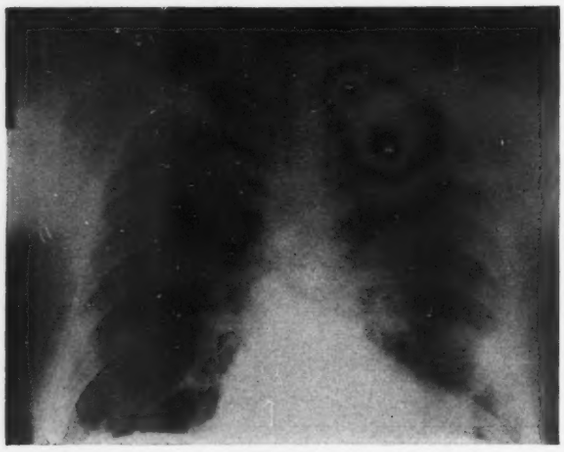


FIG. 6.

aggravated by the patient being on his feet, was relieved considerably by elevating the leg, and was of such severity as to prevent his being ambulant. The patient was admitted to the hospital on August 14, 1951.

Examination of the left leg revealed, in addition to the previously described abnormal findings, tenderness to palpation, a positive Homans' sign and distention of the superficial veins. A diagnosis of thromboangiitis obliterans with deep thrombophlebitis of the left calf veins was made and the administration of intravenous typhoid vaccine and dicumarol was initiated. Two days later a superficial thrombophlebitis of the left leg became evident. After two weeks of treatment all signs and symptoms of thrombophlebitis had subsided. The patient ceased smoking completely, as advised, was again instructed in the protection and care of his feet, and was discharged from the hospital on August 26, 1951.

When last contacted in January, 1952, he was feeling very well, had had no further thromboembolic episodes, no increase in the degree of arterial insufficiency of the extremities and was enjoying complete relief of the symptoms of esophageal hiatus hernia. He had, however, resumed smoking a few cigarettes daily during the past two months.

SUMMARY

Three cases of thromboangiitis obliterans have been presented in which at the reported stages of the disease the manifestations, in contradistinction to the common clinical course of this disease, were primarily those of a deep venous thromboembolic nature rather than occlusive arterial disease. This clinical variant, according to the literature on thromboangiitis, is rare; however, the knowledge of its possible occurrence is important to an early and correct diagnosis of the pulmonary manifestations. Other factors contributing to the confusion and delay in diagnosis of these cases were the relatively late age of the patients at the time of onset of the disease, the absence of clinical evidence of thrombophlebitis at the time of pulmonary embolization and the failure of the arterial occlusive disease to manifest activity simultaneously with the activity of thromboembolic disease.

It is possible that the age of these individuals at the time of the greatest activity of the thromboangiitis was a factor contributing to the predominantly venous thromboembolic manifestations. Certainly in general, venous thromboembolic disease is more common in the older age groups. Two of these patients were over fifty years of age at the time of onset of the thromboangiitis and all three were considerably beyond the age group in which the disease is commonly most active clinically.

The ages of Case I, fifty-two years, and Case III, fifty-seven years, together with the absence of any active thrombophlebitis or activity of the arterial disease, seemed to necessitate an investigation of the respiratory tract as the possible primary focus of their illness in spite of the knowledge that peripheral vascular disease existed.

Pulmonary embolization and infarction occurred repeatedly in all three patients while they were apparently well and ambulatory and at a time when no clinical sign of active deep or even of superficial thrombophlebitis was evident. Iliofemoral thrombophlebitis had occurred in Case I a year prior to the episodes of pulmonary embolization and recurred somewhat over a month after their cessation while in Case II iliofemoral phlebitis was evident three and one-half years before and again two and one-half months before the embolic accidents. Case III never exhibited an iliofemoral thrombophlebitis but a deep thrombosis of the foot and calf veins developed five months after the last pulmonary embolic episode. These observations would tend to confirm the statement of Allen, Barker and Hines[2] that deep thrombophlebitis of the anterior and posterior tibial veins is common in thromboangiitis but that only rarely is it clinically evident. It appears most likely that the sources of the emboli in all three cases were the calf veins rather than the more usual iliofemoral veins as suggested by Edwards.[4]

As stated by Allen, Barker and Hines[2] clinical evidences of arterial and venous involvement

are not necessarily coincident in Buerger's disease. In Cases I and III the fact that they were dissociated increased the difficulty of the differential diagnosis considerably, whereas in Case II in whom arterial occlusion had been recently active, diagnosis of the pulmonary embolic episodes was greatly facilitated by this knowledge.

The treatment of the thrombophlebitis and its attendant pulmonary embolization in thromboangiitis obliterans has not been clearly delineated in the literature. Irving Wright[5] states that there is at present no generally satisfactory treatment for recurrent, migratory thrombophlebitis and that probably the best long term therapeutic procedure is disturbance of the clotting mechanism through the effect of dicumarol, apparently in the hope that protection against embolization will be provided and that the thrombophlebitic process will subside during this period. As regards the procedure of ligation of the larger venous trunks, aside from the general objections to this procedure which have become recently evident,[6] there is reason to consider the venous congestion produced thereby specifically undesirable in Buerger's disease, in which the limb is already afflicted with an impairment of the circulatory function. Allen, Barker and Hines[2] have in their experience found that typhoid vaccine fever therapy has an almost specific effect on the superficial thrombophlebitis. If this is true it would be reasonable to expect that it might likewise exert some beneficial effect on deep thrombophlebitis.

Case I was particularly instructive as regards the efficacy of the present therapy of the deep thrombophlebitis of Buerger's disease. While the patient was receiving treatment with typhoid vaccine and while the prothrombin time was satisfactorily and continuously elevated through dicumarol, the migratory superficial phlebitis continued to involve new veins and a deep thrombophlebitis occurred. This would lend some support to the view that the pathologic process in thromboangiitis is primarily endothelial and proliferative rather than primarily thrombotic, and that possibly for this reason the phlebitis continued active in spite of the dicumarol effect which, however, was apparently sufficient to prevent the formation of a type of thrombotic material necessary for the liberation of emboli. After the quiescence of the phlebitis the patient underwent a transabdominal bilateral lumbar sympathectomy and a simultaneous vena caval ligation. Subsequent to this procedure a severe thrombophlebitis developed which almost surely involved the anastomotic and collateral veins to such a degree as to produce severe impairment of the venous return and resulted in persistent massive peripheral edema. A similar treatment and outcome had occurred in Case I reported by Kahn.[3] The possibility of immediate or long subsequent phlebitis obstructing the remaining venous channels and producing undesirable swelling would appear to be another contraindication to femoral or vena caval ligation. Surprisingly enough, the patient had an excellent result from the operative procedure as regards the arterial circulation of the extremities despite the venous obstruction.

Case II has been under continuous dicumarol therapy for four months while ambulant and has had no further thrombophlebitis or pulmonary emboli.

Case III was treated with anticoagulants and typhoid vaccine for a two-week period only while active thrombophlebitis was evident and has had no evidence of recurrent thromboembolic disease for five months. Whether one can attribute these results to therapy or to the natural course of the disease is problematic.

At present the most logical and satisfactory course of therapy for such major thromboembolic manifestations as occur in Buerger's disease would appear to be a combination of anticoagulant and intravenous typhoid therapy during the active stage of the phlebitis, with continuation of the anticoagulants indefinitely thereafter with the patient ambulant in the hope that the phlebitic process will subside. Other measures, particularly cessation of smoking, which are commonly employed in the treatment of thromboangiitis are, of course, indicated.

REFERENCES

1. Homans, J. Circulatory Diseases of the Extremities, pp. 211–255. New York, 1939. Macmillan Company.
2. Allen, E. V., Barker, N. W., Hines, E. A., Jr. Peripheral Vascular Diseases, pp. 403–471. Philadelphia, 1946. W. B. Saunders Company.
3. Kahn, J. C. Thrombophlebitis of the deep veins in thromboangiitis obliterans. *Surg., Gynec. & Obst.*, 83: 449, 1946.
4. Edwards, E. A. Phlebitis and the diagnosis of thrombo-angiitis obliterans. *Ann. Int. Med.*, 31: 1019, 1949.
5. Wright, I. S. Anti-coagulants in the treatments of thromboembolic disease. *Post Grad. Med.*, 7: 161, 1950.
6. Veal, J. R., Hussey, H. H., Barnes, E. Ligation of the inferior vena cava in thrombosis of the deep veins of the lower extremities. *Surg., Gynec. & Obst.*, 84: 605, 1947.

Physiologic Observations on a Case of Beriberi Heart Disease, with a Note on the Acute Effects of Thiamine*

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A TWENTY-NINE year old white, alcoholic male entered the hospital with all of the features of circulatory congestion of the type associated with beriberi. He showed massive edema and ascites, a dusky plethora with hot extremities and an overactive heart. The antecubital venous pressure was 310 mm. H_2O and the calcium gluconate circulation time was 9 seconds arm-to-tongue. An electrocardiogram and the size and configuration of the heart by x-ray were normal. The serum proteins were normal and there was mild anemia. Subsequent liver function studies and liver biopsy revealed moderate portal cirrhosis.

He had been drinking for several years, more heavily for the past two months, and his dietary intake had been extremely poor during this entire period. As nearly as could be determined, he had consumed only alcoholic beverages during the past six weeks.

The patient was placed on a thiamine deficient diet without salt restriction and kept at normal activity. The first physiologic study was carried out twelve hours after admission.

METHODS

Cardiac catheterization was carried out in the usual manner with the fasting patient lying recumbent. The reference level for central and antecubital venous pressures was 10 cm. from the table top. Pressure measurements were made using Sanborn electromanometers and the Poly-Viso recorder. Systolic and diastolic pressures were averaged over two respiratory cycles. Mean pressures were obtained by electrical integration. Brachial arterial pressures were measured through an indwelling arterial needle.[1] Baselines and standardizations were checked before and after each recording.

Cardiac outputs were measured by the Fick principle with the catheter in the pulmonary artery. Oxygen consumption was measured by the Benedict-Roth apparatus as blood samples were taken. Blood gas analyses were done in duplicate by the method of Van Slyke and Neill.

Serum and urine sodium determinations were carried out by the gravimetric method of Butler and Tuthill.[2] Glomerular filtration rates were measured by endogenous creatinine clearances. The creatinines were determined by the method of Peters.[3] This method is not an adsorption technic which supposedly measures "true creatinine" but its accuracy is adequate for comparison purposes as in these studies. Renal plasma flows were measured with the catheter in a renal vein by determination of the A-V creatinine extraction. A multi-holed indwelling catheter was placed in the bladder and an 800 cc. water load was administered one-half hour before the start of the study. Urine collections were made for ten- to thirty-minute periods at frequent intervals. Arterial blood samples were taken at the mid-point of collection periods.

After two control periods twenty minutes apart 140 mg. of thiamine hydrochloride were injected into the pulmonary artery. Thereafter, pressures in the pulmonary and brachial arteries

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were measured every fifteen minutes. Cardiac output determinations were made at the end of the first and second hours. One hundred mg. of thiamine hydrochloride were injected at the end of the first hour. Toward the end of the second hour the catheter was placed in a renal vein for plasma flow determination and then returned to the pulmonary artery for the remainder of the study. Deviations from this protocol during the subsequent three studies are noted in the discussion of results.

TABLE I

CIRCULATORY MEASUREMENTS—ACUTE EFFECTS OF THIAMINE*

	Normal Upper Limits	Control		15 Min.	45 Min.	60 Min.		90 Min.	120 Min.	135 Min.
Heart rate	.....	100	Thiamine 140 mg.	97	96	96	Thiamine 100 mg.	98	96	98
Brachial artery (mm. Hg)										
S/D	.....	137/75		134/72	137/73	136/71		140/79	140/82	.....
M	.....	100		98	98	96		104	102	.....
Peripheral vein (mm. H_2O)	120	310*		.....	.....	.....		.....	.....	190
Right auricle (mm. Hg)										
M	6	7		.....	.....	.....		.....	.....	7
Right ventricle (mm. Hg)										
S/D	30/6	.....		.....	.....	.....		.....	.....	32/7
M	.....	.....		.....	.....	.....		.....	.....	19
Pulmonary artery (mm. Hg)										
S/D	30/10	34/15		31/16	32/13	32/16		41/21	38/20	32/16
M	20	24		25	23	25		27	30	22

* Measured several hours prior to the study with a water manometer; final value obtained with electromanometer.

RESULTS

The control measurements (Table I) indicated borderline elevation of mean auricular pressure and more definite elevation of pulmonary artery pressures. The brachial arterial pulse pressure was wide. At the time of this first study an unusual auricular-peripheral venous pressure gradient was not anticipated. Thus the antecubital pressure was not measured at the start of the study. The pressure used as a control was measured several hours before, using a water manometer technic which in our hands produces checks with electromanometer readings within a range of 5 mm. of water.

During the first hour after the initial injection of thiamine no significant pressure changes occurred. Thirty minutes following the second injection slight pressure rises in both the brachial and pulmonary arteries were noted. One hour and fifteen minutes later the pulmonary artery pressures had returned to their previous levels. Final right heart pressures showed no change. The final antecubital venous pressure was considerably lower than that recorded several hours before the study. There was no change in heart rate throughout the procedure.

The control measurements relative to cardiac output (Table II) revealed a moderately high

TABLE II

PHYSIOLOGIC DATA—ACUTE EFFECTS OF THIAMINE

	Normal	Control		60 Min.		120 Min.
O_2 Consumption (cc./min.)	.....	(1) (2) 355 355	Thiamine 140 mg.	337	Thiamine 100 mg.	415
A-V O_2 Difference (vol. %)	.....	2.2 2.2		2.5		3.45
Arterial O_2 content (vol. %)	.....	12.9 12.9		13.1		13.1
% Saturation	.....	97		....		98
Cardiac output (L. min.)	.....	16.1 16.1		13.3		12.0
Cardiac index (L. min./M^2 BSA)	3.1 ± .4	7.8 7.8		6.5		5.8
O_2 Transport (cc./min.)	1050	2078		....		1572
O_2 Utilization (%)	20–25	17		....		26
Total peripheral resistance (dynes/sec./cm^{-5})	1512 ± 418	463		....		626

oxygen consumption, marked narrowing of the A-V oxygen difference and a very high cardiac output. The arterial oxygen content was moderately low but the saturation was normal. The total peripheral resistance was low. One hour after the initial injection of thiamine there was a trend toward lowering of the cardiac output and showed no significant change throughout the entire study period. The clearance did not suggest marked retention.

After the first dose of thiamine there was an upward trend in glomerular filtration rate and urine flow and a two-fold increase in sodium clearance. The change in clearance was opposite

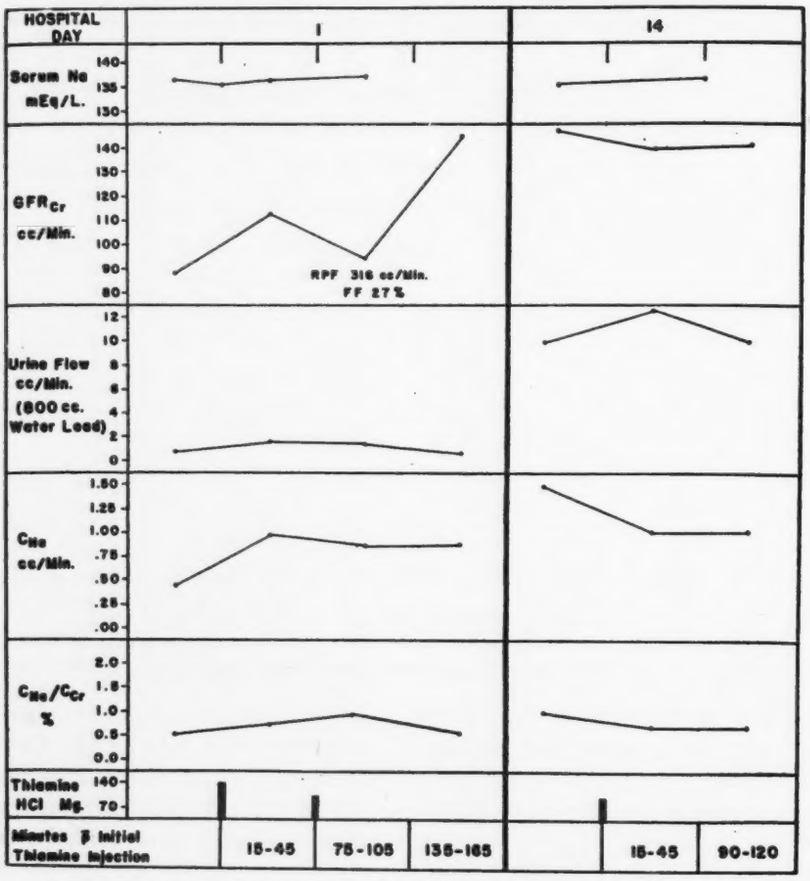

FIG. 1. Renal function data. Left hand column represents findings at the time of the first study. The right hand column indicates the data obtained two weeks later when the patient had recovered.

widening of the A-V oxygen difference but the changes were not significant. One hour after the second injection of thiamine, however, there was a marked increase in the A-V oxygen difference and oxygen consumption and a further fall in cardiac output. The peripheral resistance had increased.

The left hand side of Figure 1 presents the renal function data during the first study. The initial measurements showed a relatively low glomerular filtration rate and a markedly delayed response to water ingestion. Oliguria was persistent throughout the study period. The serum sodium was normal, 137 mEq./L., and in direction to the diurnal variation noted by Strauss and Rosenbaum.[4]

The second injection of thiamine was followed by a slight fall and then a significant rise in glomerular filtration rate into the normal range without any further rise in sodium clearance and an insignificant decrease in urine flow.

Toward the end of the second hour the catheter was introduced into the left renal vein. Renal plasma flow was 316 cc./min. Since control measurements were not made, the flow before thiamine is not known. However, the discrepancy between the renal plasma flow, which is approximately 50 per cent of normal,

and the cardiac output at about the same period, three times normal, is striking.

The patient's subsequent regimen included no specific measures aside from thiamine and niacin. He was kept at normal activity. During the first five days he lost 30 pounds in weight.

TABLE III
CIRCULATORY MEASUREMENTS AFTER TWO WEEKS OF TREATMENT WHEN PATIENT HAD RECOVERED

	Normal Upper Limits	Control	Thiamine 140 mg.	15 Min.	30 Min.	45 Min.	60 Min.
Heart rate	....	75		73	75	79	75
Brachial artery (mm. Hg)							
S/D	....	128/75		126/75	118/70	122/72	114/70
M	....	98		96	89	94	87
Peripheral vein (mm. H_2O)	120	115		.....	.....	.....	111
Right auricle (mm. Hg)							
M	6	5		.....	.....	.....	5
Right ventricle (mm. Hg)							
S/D	30/6	.....		.....	.....	.....	32/7
M	....	.....		.....	.....	.....	16
Pulmonary artery (mm. Hg)							
S/D	30/10	31/15		35/15	30/11	28/14	32/14
M	20	21		22	17	17	19

At the end of ten days he had lost 40 pounds and all clinical manifestations of congestion had disappeared. Urinary chloride excretion showed a steady rise during this period as did urine volume. At least 80 per cent of the fluid loss may be assumed to have come from the extracellular space; and since the serum sodium remained constant, sodium loss was proportionate to water loss.[5,6]

He was re-studied two weeks after entry. (Table III.) Control circulatory measurements revealed narrowing of the arterial pulse pressure and decrease in the heart rate. The antecubital venous pressure was normal and the right auricular and pulmonary artery pressures were slightly lower. After the injection of thiamine there was a trend toward lower pressures in the brachial artery over the next hour. No other changes were noted. The right ventricular pressures registered at the end of the procedure were the same as those of the first study.

The control cardiac output (Table IV) was much lower. Oxygen consumption was decreased and the A-V oxygen difference was further increased. The total peripheral resistance had increased to normal. After administration of thiamine there was no change in the measurements except for an apparent increase in the arterial oxygen content. We are unable to account for this on any physiologic basis and are inclined to attribute it to an error in collection of the control sample, since a determination the following day of 17.20 volumes per cent

TABLE IV
PHYSIOLOGIC DATA AFTER TWO WEEKS OF TREATMENT WHEN PATIENT HAD RECOVERED

	Normal	Control	Thiamine 140 mg.	60 Min.
O_2 Consumption (cc./min.)	.....	274		274
A-V O_2 difference (vol. %)	.....	3.51		4.23
Arterial O_2 content (vol. %)	.....	16.49		17.16
% Saturation	.....	95		98
Cardiac output (L./min.)	.....	7.8		6.5
Cardiac index (L./min./M^2BSA)	3.1 ± .4	4.2		3.5
O_2 Transport (cc./min.)	1050	1288		1113
O_2 Utilization %	20–25	21		25
Total peripheral resistance (dynes/sec./cm^{-5})	1512 ±418	1430		1040

checked with the previous value of 17.16 volumes per cent.

The renal function data on this occasion (Fig. 1) showed a high urine flow with respect to the same 800 cc. water load. The glomerular filtration rate was the same as at the end of the acute study two weeks previously and the sodium clearance was somewhat higher. After thiamine there was no change in filtration rate or urine flow but sodium clearance fell. It is difficult to interpret this clearance change although it was in the direction of expected diurnal variation. Efforts to catheterize a renal vein for blood flow determination were not successful.

A third catheterization was attempted four weeks after entry but the catheter could not be passed beyond the right auricle. It is significant, however, that the mean auricular pressure was unchanged. The A-V oxygen difference showed still further increase and the cardiac output and oxygen consumption were within normal limits.

The patient was discharged at the end of six

weeks. When he returned for follow-up one week later, he was intoxicated. There was, however, no edema or increase in weight.

A fourth study was made several days later. (Table v.) The catheter could not be passed beyond the right ventricle and output was

TABLE V

DATA OBTAINED SEVEN WEEKS AFTER INITIAL TREATMENT

Peripheral vein (mm. H_2O)	105
Right auricle (mm. Hg)	5
Right ventricle S/D	34/8
M	14
Cardiac output (L./min.)	12.3
A-V O_2 Diff. (vol. %)	2.72
GF_{cr} (cc./min.)	125
RPF (cc./min.)	570

measured using right auricular blood. It will be noted that there was return of a high cardiac output and small A-V oxygen difference but persistence of the same pressure relationships. On this occasion renal hemodynamics were near normal and there were no features of congestion. However, the patient's lack of diuretic response to 800 cc. of water was similar to that of the first study.

COMMENTS

The acute effects of thiamine in this case, as observed over a two-hour period, were, in general, what would be expected on the basis of earlier observations by Weiss and Wilkins[7] and by Porter and Downs.[8] The increase in oxygen consumption is of some interest. It would seem to represent improved oxygen utilization preceding decrease in circulatory work of a magnitude sufficient to lower over-all oxygen needs.

The increases in glomerular filtration rate and sodium clearance, the persistence of oliguria and their lack of correlation are of particular interest. An increase in renal blood flow and/or efferent arteriolar constriction could explain the rise in filtration rate but it would seem necessary to postulate factors other than renal hemodynamics to explain the handling of sodium and water.

In 1947 Burwell and Dexter[9] reported the first case of so-called beriberi heart disease investigated by the cardiac catheterization technic. They did their studies before treatment and one month later, and demonstrated many of the phenomena which characterize the case just presented. Their data relative to central pressures, however, differ markedly from those of the present case. Before treatment there was two-fold elevation of right ventricular and pulmonary artery pressures which after one month had fallen to approximately normal levels.

In contrast, the right heart and pulmonary artery pressures in our case were only slightly above the limits found in eight resting normals by Dexter,[10] and below the levels seen at comparable flow rates in exercising normals. One of Dexter's subjects increased his mean auricular pressure from 6 mm. Hg to 9 mm. Hg on exercise as his cardiac index rose from 4.6 to 5.4. Another showed a rise from 13 mm. Hg to 29 mm. Hg in pulmonary artery mean pressure as his cardiac index increased from 4.2 to 6.9. That elevations of right ventricular filling pressure may reflect increased flow rather than decompensation was also noted by Cournand.[11]

Two other findings in our study are of importance in this connection. The auricular-peripheral venous pressure gradient was the reverse of that seen in right heart failure.[12] Further, in terms of pressure work and velocity work done at a given filling pressure, the right ventricle performed more efficiently before treatment when the cardiac output was 16 L. per minute than during recovery when the flow had fallen to 8 L. per minute.[13]

Heart failure is frequently only demonstrated by the measurement of abnormal filling pressure during exercise or other stress. However, normal pressure at rest with rise to abnormal levels on exercise has not been described in patients with frank peripheral congestion and edema at rest.

In view of these observations it is illogical to postulate myocardial failure as the basis for the congestive state in this patient. The normal, unchanging heart size and serial electrocardiograms support this conclusion.

The other comparable cardiodynamic studies available[6,9,16] have documented the presence of frank myocardial failure in beriberi. This is neither contradictory nor surprising since the huge inflow load added to derangement of myocardial metabolism would be expected to embarrass the heart eventually. On the other hand, it is noteworthy that clinical reports on beriberi include other instances of normal sized hearts in the presence of congestion and edema.[7,17,18]

The fall of peripheral venous pressure after thiamine administration, with the mean auricular pressure remaining constant, suggests that the peripheral venous hypertension present initially was largely the result of transmission of arterial pressure through the dilated arteriolar bed. Hypervolemia was undoubtedly present before treatment;[8] but when this is sufficient to produce elevated peripheral venous pressure, its effect is equally apparent in the right auricle.[14] The same would be true of generalized changes in venous tone.[15]

The over-all data on renal function are of considerable interest. The initial grossly abnormal pattern is in marked contrast to the relative normality of the cardiac findings and the changes toward normal do correlate with the disappearance of congestion although the exact sequence cannot be discerned. The patient's exaggerated diuretic response to 800 cc. of water after treatment differs strikingly from the oliguric response before treatment. The patient was not clinically dehydrated at any time and neither sodium intake nor time of study appear to explain the differences seen. Although variations in diuretic response to water ingestion can be seen in the same person from day to day,[19] the changes seen here are extreme. The initial picture suggests excess posterior pituitary effect, while the recovery pattern was compatible with a relative posterior pituitary deficient state, perhaps a compensatory recovery mechanism. Any role the patient's liver disease may have played is similarly speculative.

The majority of studies on the genesis of edema and its temporal relationship to heart failure have been attempts to prove the presence of a system of constant sequential causes and effects. It has become increasingly apparent that neither the backward nor forward failure theory, as usually stated, satisfactorily explains all the situations encountered clinically and experimentally. This was pointed up anew by the studies of Ellis and his associates.[20] They observed peripheral edema in five patients with uncomplicated mitral stenosis despite the presence, at rest and after exercise, of normal right heart or peripheral venous pressures. Three had low cardiac output at rest but in two the output was well maintained after exercise. These findings could not be explained.

The outlines of a mechanism which may be the common denominator have appeared in work which indicates that the volume or distribution of blood in specific areas has a profound effect on the body's handling of salt and water. Alteration in regional flow commonly is evident in the kidney in the usual etiologic types of heart failure.[21] Variations in posture and compression of the neck have been shown to influence salt and water metabolism.[22–24] Occlusion of the inferior vena cava either above or below the renal veins with resultant segregation of blood has been shown to decrease sodium and water excretion markedly.[25] Hypervolemia is an early consequence of arteriovenous fistula.[26,27] The present study illustrates another condition characterized by hypervolemia and edema in which the basic circulatory defect is distribution of flow. In this instance the heart maintained its efficiency in moving the increased venous return along.

Comparison between arteriovenous fistula and the vascular abnormality in beriberi has frequently been made. Apart from metabolic considerations, the basic difference between the two lies in the nature of the "shunt." In fistula the connection is direct from artery to vein; in beriberi it is through the dilated capillaries. In fistula the shunt is localized and the venous valves and collateral veins combine to block widespread transmission of arterial pressure; in beriberi the defect is generalized, at least in the extremities. Thus the capillaries are not protected and there are no unaffected collateral veins. Evidence relative to the presence of altered capillary permeability is inconclusive.[7,28]

These differences adequately explain why venous hypertension and edema may develop in beriberi without myocardial failure. In arteriovenous fistula, because of the protective mechanisms present, edema does not develop until the right heart is embarrassed by an excessive inflow load. In beriberi, however, the high capillary pressure fosters the development of edema at the outset.

Our findings tend to support the thesis that the prime factor in the retention of sodium and water is related to changes in blood volume or flow in certain strategic areas whether mediated by right heart failure, left heart failure, peripheral factors or by combinations of the three. Moreover, regions other than the kidney, for example, the adrenal and the posterior pituitary, are important in this mechanism and the volume-flow defect may conceivably vary in degree and location from case to case. In this may be the explanation for some of the dis-

crepancies in reported studies attempting to correlate cardiac and renal hemodynamics in congestive heart failure.

The appearance of overt edema is not a simple predictable consequence of sodium and water retention but depends upon disturbance of the Starling equilibrium. Capillary hypertension may result from severe hypervolemia, venous hypertension secondary to right heart failure, arteriolar dilatation or combinations of these factors. Other factors which may operate are decrease in the colloid osmotic pressure of the blood and increase in capillary permeability. Once transudation begins it is logical to assume that it may initiate or further aggravate the volume-flow defect which appears to be the stimulus for retention of sodium and water.

When one considers the complex combinations of factors which may exist, it is not surprising that limited studies attempting to show constant time relationships between heart failure, venous hypertension, cardiac output, renal blood flow, retention of salt and water, hypervolemia and edema have produced conflicting and confusing results.

SUMMARY AND CONCLUSIONS

A case of beriberi with massive edema and venous hypertension was studied before treatment and on three occasions during recovery.

The cardiodynamics found were compatible with the increased rate of blood flow and did not indicate the presence of myocardial failure. The auricular-peripheral venous pressure relationship before and after treatment with thiamine was the reverse of that seen in right heart failure and suggested transmission of arterial pressure through the dilated arteriolocapillary bed.

Renal hemodynamics showed a marked decrease in blood flow initially with rise during recovery. The glomerular filtration rate and sodium clearance were low before thiamine and rose later. There was marked water retention before treatment and high urine flow during recovery. No definite correlations could be made from the available data.

The mechanisms of venous hypertension and edema in beriberi are discussed in relationship to the general problem of edema in heart failure. The probable importance of disturbed volume-flow in the mechanism of sodium and water retention is stressed.

REFERENCES

1. Arst, D. B., Silver, M. and Lahey, W. J. The use of vinyl plastic tubing in recording pressure phenomena. *Am. Heart J.*, 42: 746, 1951.
2. Butler, A. M. and Tuthill, E. An application of the uranyl zinc acetate method for determination of sodium in biological material. *J. Biol. Chem.*, 93: 171, 1931.
3. Peters, J. H. Determination of creatinine and creatine in blood and urine with photoelectric colorimeter. *J. Biol. Chem.*, 146: 179, 1942.
4. Strauss, M. B., Rosenbaum, J. D. and Nelson, W. P. The effect of alcohol on the renal excretion of water and electrolyte. *J. Clin. Investigation*, 29: 1053, 1950.
5. Iseri, L. T., Boyle, A. J. and Myers, G. B. Water and electrolyte balance during recovery from severe congestive failure on a 50 mg. sodium diet. *Am. Heart J.*, 40: 706, 1950.
6. Uhl, H. M. S., Alexander, L. C., McCaughey, R. S., Boyle, A. J., Iseri, L. T. and Myers, G. B. Fluid and electrolyte balance during recovery from high output failure due to beriberi. *Proc. Am. Fed. Clin. Res.*, Atlantic City, N. J., May 1, 1951.
7. Weiss, S. and Wilkins, R. W. The nature of cardiovascular disturbances in nutritional deficiency states (beriberi). *Ann. Int. Med.*, 11: 104, 1937.
8. Porter, R. R. and Downs, R. S. Some physiological observations on circulation during recovery from vitamin B_1 deficiency. *Ann. Int. Med.*, 17: 645, 1942.
9. Burwell, C. S. and Dexter, L. Measurements of circulation in beriberi heart disease. *Tr. A. Am. Physicians*, 60: 59–61, 1947.
10. Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R. and Sawyer, C. G. Effect of exercise on circulatory dynamics of normal individuals. *J. Appl. Physiol.*, 3: 439, 1951.
11. Cournand, A., Baldwin, J. S. and Himmelstein, A. Cardiac Catheterization in Congenital Heart Disease. New York City, 1949. Commonwealth Fund.
12. Bloomfield, R., Lawson, H., Cournand, A., Breed, E. and Richards, D. W., Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. *J. Clin. Investigation*, 25: 639, 1946.
13. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W. and Dexter, L. Studies of the circulatory dynamics in mitral stenosis. II. Altered dynamics at rest. *Am. Heart J.*, 41: 30, 1951.
14. Huckabee, W., Casten, G. and Harrison, T. R. Experimental hypervolemic heart failure: its bearing on certain general principles of heart failure. *Circulation*, 1: 343, 1950.
15. Michael, J. Cardiac venous congestion: its causes and consequences. *Am. J. Med.*, 6: 651, 1949.
16. Campbell, J. A., Selverstone, L. A. and Donovan, D. L. Studies on the high output failure of occidental beriberi. *Proc. Am. Soc. Clin. Invest.*, April 30, 1951.
17. Jolliffe, N. and Goodhart, R. Beriberi in alcohol addicts. *J. A. M. A.*, 111: 380, 1938.

18. Ungley, C. C. The clinical manifestations of vitamin B deficiency. *Newcastle, M. J.*, 19: 43, 1939.
19. Storey, W. E. Variations in urinary dilution and concentration among healthy males under simple standard conditions. *Ann. Int. Med.*, 34: 737, 1951.
20. Ellis, L. B. et al. Studies in mitral stenosis. I. A correlation of physiologic and clinical findings. *Arch. Int. Med.*, 88: 515, 1951.
21. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
22. Lewis, J. M., Jr., Buie, R. M. Sevier, S. M. and Harrison, T. R. The effect of posture and of congestion of the head on sodium excretion in normal subjects. *Circulation*, 2: 822, 1950.
23. Viar, W. N. Oliver, B. B., Eisenberg, S., Lombardo, T. A., Willis, K. and Harrison, T. R. The effect of posture and of compression of the neck on excretion of electrolytes and glomerular filtration: further studies. *Circulation*, 3: 105, 1951.
24. Lombardo, T. A., Eisenberg, S., Oliver, B. B., Viar, W. N., Eddleman, E. E., Jr. and Harrison, T. R. Effects of bleeding on electrolyte excretion and on glomerular filtration. *Circulation*, 3: 260, 1951.
25. Farber, S. J., Alexander, J. D. and Eichna, L. W. Renal hemodynamics and salt and water excretion during induced congestion of the inferior vena cava. *Proc. Am. Soc. Clin. Invest.*, April 30, 1951.
26. Lillehei, C. W., Babb, J. R. R. and Visscher, M. B. Effect of Arteriovenous Fistulas upon Pulmonary Arterial Pressure, Cardiac Index, Blood Volume and Extracellular Fluid Space. Surgical Forum, p. 275. Philadelphia, 1951. W. B. Saunders.
27. Warren, J. V., Elkin, D. C. and Nickerson, J. L. The blood volume in patients with arteriovenous fistulas. *J. Clin. Investigation*, 30: 220, 1951.
28. Swank, R. L. and Bessey, O. A. Production and study of cardiac failure in thiamine-deficient pigeons. *Arch. Int. Med.*, 70: 763–766, 1942.

Hemochromatosis after Prolonged Oral Iron Therapy in a Patient with Chronic Hemolytic Anemia*

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THE interest in the case described herein centers about the association of chronic hemolytic anemia with hemochromatosis in a patient who took approximately 1,600 gm. of iron by mouth as a placebo during a period of twelve years. He received transfusions only terminally.

Increased hepatic storage iron has been observed in untreated, pernicious anemia and in hemolytic anemia.[1,2] The excess iron is usually limited to 1 or 2 gm.,[3] compared to the normal storage 0.3 to 0.5 gm.,[4] is seen at first only in the reticuloendothelial cells and probably represents the amount of iron deviated from the circulating blood. Large iron deposits in the liver parenchyma are found in these patients usually only after multiple transfusions.[5]

Massive parenchymal iron deposition in the absence of administration of iron or blood is seen clinically in idiopathic hemochromatosis[6] and in South African natives on deficient diets.[7]

The total body iron of about 4.5 gm. is maintained largely by regulation of absorption; of the 5 to 17 mg. of iron in the normal diet an average of only 10 per cent is assimilated daily; less than 1 mg. is normally lost from the body every day.[8,9] Even excessive hemolysis does not cause increased loss of iron. It has been shown in polycythemic subjects treated with acetylphenylhydrazine that with the daily liberation of as much as 192 mg. of iron from the hemolyzed erythrocytes excretion remained below 1 mg.[10]

That increased absorption of iron in chronic anemias other than hypochromic anemias may lead to excessive body iron is suggested by the discovery in cases of hemolytic and refractory anemias[11] of liver iron in excess of the amounts that could be accounted for by transfusion iron. Isotope tracer studies in these conditions show assimilation of considerable quantities of the metal despite adequate or increased iron stores.[12] Increased retention of large oral doses has been reported in normal subjects by balance studies.[13,14]

Experimentally, excessive deposition of iron in the liver has been produced in rats fed diets deficient in phosphorus with added iron, and in rats[15] or rabbits[16] fed normal diets with large amounts of added iron.

CASE REPORT

Mr. J. J. was an unemployed carpenter, aged seventy-three, who had been under medical observation from 1935 to 1951. He entered the Boston City Hospital on February 16, 1951, because his chronic cough had recently become much worse, was productive of greenish sputum, and because there had been severe dyspnea and some ankle swelling.

Detailed hematologic data had been obtained on this patient since 1935 when anemia, acholuric jaundice, reticulocytosis and increased erythrocyte osmotic fragility were noted. During the subsequent years he had four attacks of severe, steady pain in the right upper quadrant lasting one to two days, nausea, vomiting, chills, prostration and severe jaundice, associated with bilirubinuria, lasting seven to ten days. These attacks had been diagnosed as biliary colic with partial obstruction of the common bile duct. The patient had refused splenectomy through-

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out the years of observation; the jaundice had been constant and of a mild to moderate degree; his urine, acholuric.

An attack of abdominal pain in 1949 led to a cholecystotomy. The gallbladder was found to be distended, containing some clear bile, inspissated material but no stones. A liver biopsy was interpreted as showing "pigment cirrhosis."

The patient had received digitalis, gr. 1½ daily, since 1944 for congestive failure, thought to be due to arteriosclerotic heart disease, and terpin hydrate, 5 ml., three to four times daily for a chronic cough. He was given ferrous sulfate, gr. 3, two times daily as "placebo" from 1937 to 1949 (a total of about 1,500 gm. or about 500 gm. metallic iron). He was not known to have received a transfusion prior to his final hospital admission.

The patient was born in Syria in 1878, immigrated to the United States at the age of nineteen and had worked until his present illness. He had been separated from his wife for many years and lived alone in a furnished room, obtaining fairly adequate meals in restaurants. He knew little about his family. Hematologic studies, including osmotic and mechanical erythrocyte fragility tests, on one daughter, a nephew and a niece were negative.

At physical examination on entry his temperature was 101.3°F. Pulse was 90/minute; respirations, 30/minute; blood pressure, 110/45 mm. Hg; weight 142 pounds. The patient was a thin, dyspneic, elderly man appearing chronically and acutely ill. He had slightly icteric scleras, dark skin suggesting a deep suntan and several small areas of diffuse, brown-black pigmentation on the hard palate. The lymph nodes were not enlarged. Over the right posterior lung field there were diminished diaphragmatic excursion, dullness, decreased breath sounds and subcrepitant rales. He had an enlarged heart, with auricular fibrillation, a grade III systolic apical murmur over the entire precordium, but not transmitted to the neck; A2 was louder than P2. The neck veins were distended 2 cm. above the clavicle in sitting position. Both liver and spleen were palpable as firm, smooth, non-tender masses extending two fingerbreadths past the umbilicus. Edema, most marked over the ankles, extended to the mid-back. Examination of the genitalia, rectum and nervous system was not remarkable.

The usual levels of the blood had been as follows: red cells 3–3.5 by 10^6/mm.^{3}; hemoglobin 9–10 gm./100 ml.; hematocrit 27–35 per cent; mean corpuscular volume 86–96/μ^3; mean corpuscular hemoglobin concentration 29–30 per cent; reticulocytes 8–14 per cent; white cells 7–14 by 10^3/mm.^{3}; icterus index 5–25 units; indirect bilirubin 4–5 mg./100 ml.; osmotic fragility; hemolysis beginning at 0.60 per cent sodium chloride with 50 per cent hemolysis at 0.40 (normal beginning at 0.42–0.49, with 50 per cent hemolysis at 0.33–0.41); mechanical fragility 10 per cent (normal 2–5 per cent). Bone marrow examination had shown increased erythropoiesis with normoblasts predominating; Coombs' tests had been negative. The urine had shown a maximum specific gravity of 1.018, no albumin or increased urobilinogen, no abnormality of the sediment and bile only during biliary colics. The stool had contained pigment even during the biliary colics; it had never contained blood. The plasma proteins, liver function tests, non-protein nitrogen, fasting blood sugars had been normal in recent years; serum iron in 1949 was 209 μg./100 ml.

In the hospital the cough, fever, dyspnea and edema persisted in spite of penicillin, aureomycin, streptomycin and frequent injections of mercuhydrin. On the twenty-first hospital day a particularly severe abdominal pain developed and peristalsis ceased. At surgery there was some distention of the small and large bowels but no obstruction or apparent inflammation; the gallbladder was opened and gravel scooped out. The patient received a total of 2,000 ml. of whole blood but continued to do poorly and died the day after operation, March 31, 1951.

Clinical diagnosis: congenital hemolytic anemia (hereditary spherocytosis), hemochromatosis, cholecystitis and cholelithiasis, arteriosclerotic heart disease, bronchopneumonia.

The autopsy* report (only the pertinent findings of the postmortem will be described) revealed the peritoneal cavity contained approximately 1,000 ml. of serosanguinous fluid. The pleural cavities contained approximately 500 ml. of clear, serous fluid on each side. The lungs weighed 860 gm. on the right and 600 gm. on the left (usual weight 300 to 350 gm.). Bilateral congestion and edema of the lower lobes were present and there was exudate in the right lower lobe bronchioles. The heart weighed 460 gm. (normal weight 350 to 400 gm.). The myocardium showed brownish pigmentation. A

* Performed by Dr. Leo Blank.

moderate degree of sclerotic fibrosis of the aortic and mitral valves was present. The coronaries showed arteriosclerosis without occlusion.

The spleen weighed 1,780 gm. (normal weight 250 gm.). The capsule showed gray-white thickening and opacity. On section the splenic substance was firmer than usual and red-brown in color. The trabecular and follicular markings were indistinct. The splenic artery and vein were present. Iron analysis is given in Table 1. The liver was markedly enlarged and weighed 2,740 gm. (normal weight 1,500 gm.). The capsule was thickened, somewhat opaque and dull gray. A distinct, uniform, fine nodularity was present in which the individual nodules varied from 3.0 to 5.0 mm. in diameter. On section this pattern of nodularity was present throughout, and the liver substance had a red-brown color. (Table 1.) The gallbladder was edematous, thickened up to 5.0 mm. and contained a few small, black, pigment stones. Similar stones were found within the biliary tree. None of these produced obstruction to the flow of bile.

TABLE 1
CHEMICAL IRON IN ORGANS

	Concentration * of Iron mg./gm.		Total Iron gm./organ
	Dry Ashing	Wet Ashing	
Patient			
Liver	13.201	3.221	8.8
Spleen	16.534	3.814	6.85
Normal Subject			
Liver	<.1[17]	.225*	<1.5[19]
Spleen	1.37[18]	.269*	

* Iron analyses on the unfixed, unperfused tissues were performed by Dr. S. Finch.

The adrenals were slightly smaller than usual. There was distinct dark brown coloration within the cortex almost totally obscuring the usual bright yellow (lipochrome). The genital organs were not remarkable except for some atrophy and apparent fibrosis of the testes, consistent with the patient's age. No pigmentation was present. The bone marrow appeared somewhat browner than usual and was not increased in amount.

On microscopic examination diffuse, fine, fibrous scarring was found to be present throughout the liver, extending out from the portal triads. These scars did not entirely interconnect. The intervening hepatic parenchyma appeared well preserved without significant distortion of the lobular architecture. Prominent golden brown pigmentation giving positive iron stain was present throughout. It was most abundant within the Kupffer cells, occurred in the fibrous scars in irregular masses, chiefly extracellular, but also in the parenchymal cells. Special stains revealed small amounts of hemofuscin. (Fig. 1.)

The spleen showed over-all congestion as well as marked fibrosis and thickening of the septal walls. The sinuses were narrowed and lined by moderately hypertrophied endothelial cells. Throughout the section there was extensive hemosiderin within the lining cells of the sinuses and in large aggregations within the thickened septal walls. There were no abnormalities of the splenic vessels and no evidence of extramedullary hematopoiesis or of erythrophagocytosis.

The pancreas showed diffuse, chiefly interstitial edema and infiltration of polymorphonuclear cells. The islets were well preserved. Widely scattered focal collections of hemosiderin were found within occasional acinar cells. No pigmentation was present in the islets. Hemofuscin was demonstrated within the smooth muscle of the walls of the pancreatic ducts.

The lymph nodes varied in the amount of pigment found. Nodes from the mesentery and from the porta hepatic region contained moderate amounts of hemosiderin in the lining of the sinusoidal walls and in occasional macrophages in the pulp. The hilar nodes contained only minimal amounts of hemosiderin. There was no evidence of erythrophagocytosis.

The bone marrow was markedly cellular, showing active hemopoiesis in both the red and white series. Scattered foci of iron pigment were evident chiefly within the stromal fibroblasts.

The adrenals contained increased pigmentation of the zona reticularis with clumped masses of hemosiderin between the cells of the fasciculi. Hemofuscin could likewise be demonstrated within the adrenal. In the skin a rare focus of hemosiderin was found in the subcutaneous tissue, chiefly about the adnexal glands and hair shafts. The kidney sections demonstrated scattered pigmentations of the epithelium of the convoluted tubules. The thyroid, pituitary,

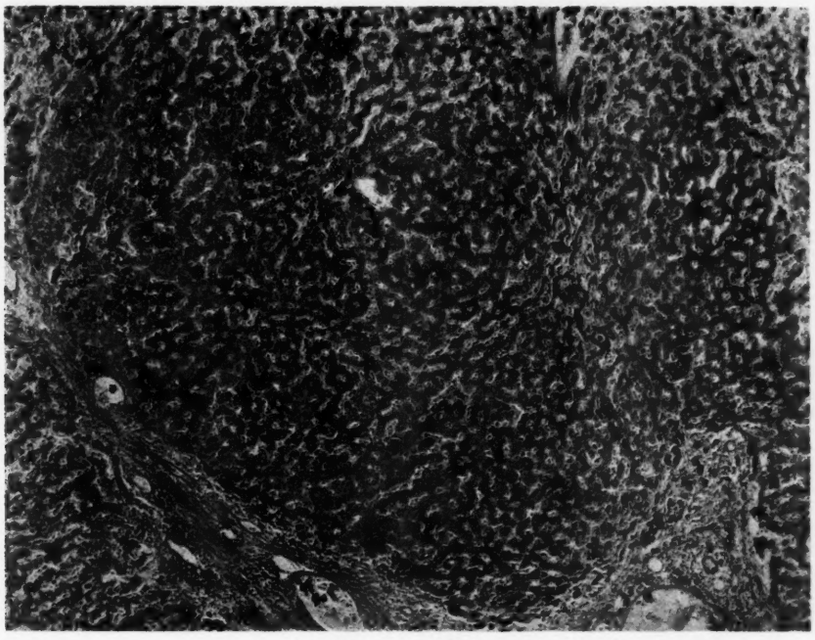

FIG. 1. Low power view of liver lobule showing increase of periportal connective tissue; dark granules are hemosiderin.

testes and intestinal mucosa all failed to demonstrate pigmentation and were otherwise not remarkable. The gross impression of acute cholelithiasis superimposed on a chronic cholecystitis was confirmed by a microscopic examination.

The anatomic diagnoses were as follows: (1) Pigment cirrhosis of the liver (hemosiderin and hemofuscin) with pigmentation of pancreas, bone marrow, adrenals, renal tubules and skin; (2) acute cholecystitis superimposed on chronic cholecystitis with cholelithiasis; (3) acute interstitial pancreatitis; (4) arteriosclerotic heart disease; (5) pulmonary congestion and edema; and (6) acute bronchitis.

COMMENT

The regulation of iron absorption is highly controversial. The status of storage iron, as reflected in gastrointestinal[20] mucosal ferritin, is thought to regulate this absorption. According to Granick,[21] Fe^{++} in the mucosal wall of the upper small intestine combines with iron-free protein, apoferritin, to form ferritin. When the protein is saturated, Fe^{++} accumulates in the mucosal cells and then blocks further movement of Fe^{++} from the lumen into the intestinal wall.

In addition to this concept other theories postulate that the amount of iron available in food and medications affects absorption. Achlorhydria, alkaline medications[22,23] and high phosphorus[24] may decrease available food iron. Large doses of oral iron may be retained in excess regardless of body iron stores,[12] hemoglobin level or achlorhydria.[14] Low phosphorus diet[15] may also increase absorption.

Iron given by injection or in transfusions is retained by the body almost completely unless there is bleeding. When iron is given parenterally, tissue overload and harmful effects may result.[25]

A distinction is often drawn between hemosiderosis and hemochromatosis. In hemosiderosis the pigment is usually limited to the reticuloendothelial system and the liver parenchyma; the increased iron stores are secondary to increased erythrocyte destruction or multiple transfusions and are of little clinical significance.[25] Hemochromatosis is characterized clinically by cirrhosis, diabetes mellitus and eunuchoid changes, pathologically by extensive deposition in parenchymal cells of many organs and in reticuloendothelial cells throughout the body of ferric hydroxide polymers in the form of brown granules called hemosiderin, cirrhosis and an iron-free pigment, hemofuscin.[5] On clinical[5,13] and experimental[15,16] evidence the difference between hemosiderosis and hemochromatosis may well be a quantitative rather than a qualitative one. However, the complete

pattern of classic hemochromatosis has not as yet been described in any single instance of exogenous hemochromatosis.[5]

The chief cause of this patient's increased iron absorption was probably his large oral intake; the chronic hemolytic anemia may have been contributory. The daily dose of ferrous sulfate was about 360 mg. (gr. iii twice a day) equivalent to 120 mg. of elemental iron. Analyses of the liver and spleen showed a total of over 15 gm. of iron. (Table 1.) This may represent assimilation of 3 per cent of oral iron medication or about 3.5 mg. daily for twelve years. At autopsy large amounts of hemosiderin were demonstrated in most of the organs, hemofuscin in the liver, pancreas and adrenals; there was cirrhosis of the liver. Because of the distribution and the quantity of iron found, the diagnosis of hemochromatosis was made.

These findings suggest that prolonged oral iron medication in a patient who is not iron deficient and who is not losing blood may lead to great iron excess and structural changes in the tissues. They also offer additional evidence that hemosiderosis and hemochromatosis may be closely related.

SUMMARY

1. The clinical history and autopsy findings are given of a patient with congenital hemolytic anemia who took a large amount of oral iron medication during his lifetime.

2. Possible pathogenesis of the patient's hemochromatosis is discussed.

REFERENCES

1. Ryffel, J. H. The amount of iron in the organs in cases of pernicious anemia. *J. Path. & Bact.*, 14: 411, 1910.
2. Muir, R. and Shaw Dunn, J. Retention of iron in organs in haemolytic anemia. *J. Path. & Bact.*, 19: 417, 1914.
3. Finch, C. A., Hegsted, D. M., Kinney, T. D., Thomas, E. D., Rath, C. E., Harkins, D., Finch, S. and Fluharty, R. G. Iron metabolism. *Blood*, 5: 983, 1950.
4. Sheldon, J. H. Hemochromatosis. New York, 1935. Oxford University Press.
5. Schwartz, S. V. and Blumenthal, S. A. Exogenous hemochromatosis resulting from blood transfusions. *Blood*, 3: 617, 1948.
6. Granick, S. Iron metabolism and hemochromatosis. *Bull. New York Acad. Med.*, 25: 403–428, 1949.
7. Gillman, J. and Gillman, T. Structure of the liver in pellagra. *Arch. Path.*, 40: 239–263, 1945.
8. Wintrobe, M. M. Clinical Hematology, 3rd ed. Philadelphia, 1951. Lea & Febiger.
9. Drabkin, D. L. Metabolism of the hemin chromoproteins. *Physiol. Rev.*, 31: 345, 1951.
10. McCance, R. A. and Widdowson, E. M. Fate of elements removed from blood stream during treatment of polycythaemia by acetyl-phenylhydrazine. *Quart. J. Med.*, 6: 277, 1937.
11. Muirhead, E. E. Iron overload aggravated by blood transfusions. *Arch. Int. Med.*, 83: 477, 1949.
12. Dubach, R., Callender, S. T. and Moore, C. V. Studies on iron transport and metabolism. VI: Absorption of radioactive iron in patients with fever and with anemias of varied etiology. *Blood*, 3: 526, 1948.
13. Brock, J. F. and Hunter, D. The fate of large doses of iron administered by mouth. *Quart. J. Med.*, 6: 5, 1937.
14. Barer, A. P. and Fowler, W. M. Influence of gastric acidity and degree of anemia on iron retention. *Arch. Int. Med.*, 59: 785, 1937.
15. Hegsted, D. M., Finch, C. A. and Kinney, T. D. The influence of diet on iron absorption. *J. Exper. Med.*, 90: 147, 1949.
16. Polson, C. J. The storage of iron following its oral and subcutaneous administration. *Quart. J. Med.*, 23: 77, 1929.
17. Gillman, J., Mandelstam, J. and Gillman, T. Comparison of chemical and histological estimations of iron and copper contents of liver of Africans in relation to pathogenesis of cytosiderosis and hemochromatosis. *South Africa J. M. Sc.*, 10: 109, 1945.
18. Sandberg, M., Gross, H. and Holly, O. M. Changes in retention of copper and iron in liver and spleen in chronic diseases accompanied by secondary anemia. *Arch. Path.*, 33: 834, 1942.
19. Heath, C. W. and Patek, A. J. The anemia of iron deficiency. *Medicine*, 16: 267–350, 1937.
20. Hahn, F. F., Bale, W. F., Lawrence, E. O. and Whipple, G. H. Radioactive iron and its metabolism in anemia. *J. Exper. Med.*, 69: 739, 1939.
21. Granick, S. Ferritin. *J. Biol. Chem.*, 164: 737, 1946.
22. Kellogg, F. and Mettier, S. R. Utilization of dietary iron in the regeneration of hemoglobin. *Arch. Int. Med.*, 58: 278, 1936.
23. Mettier, S. R. and Minot, G. R. The effect of iron on blood formation as influenced by changing the acidity of the gastroduodenal contents in certain cases of anemia. *Am. J. M. Sc.*, 181: 25, 1931.
24. Fuhr, I. and Steenbock, H. The effect of dietary calcium, phosphorus, and vitamin D on the utilization of iron. *J. Biol. Chem.*, 147: 59, 1943.
25. Clough, P. W. Hemosiderosis and the parenteral administration of iron. *Ann. Int. Med.*, 36: 694, 1952.
26. Lichtman, S. S. Diseases of the Liver, 2nd. ed. Philadelphia, 1949. Lea & Febiger.

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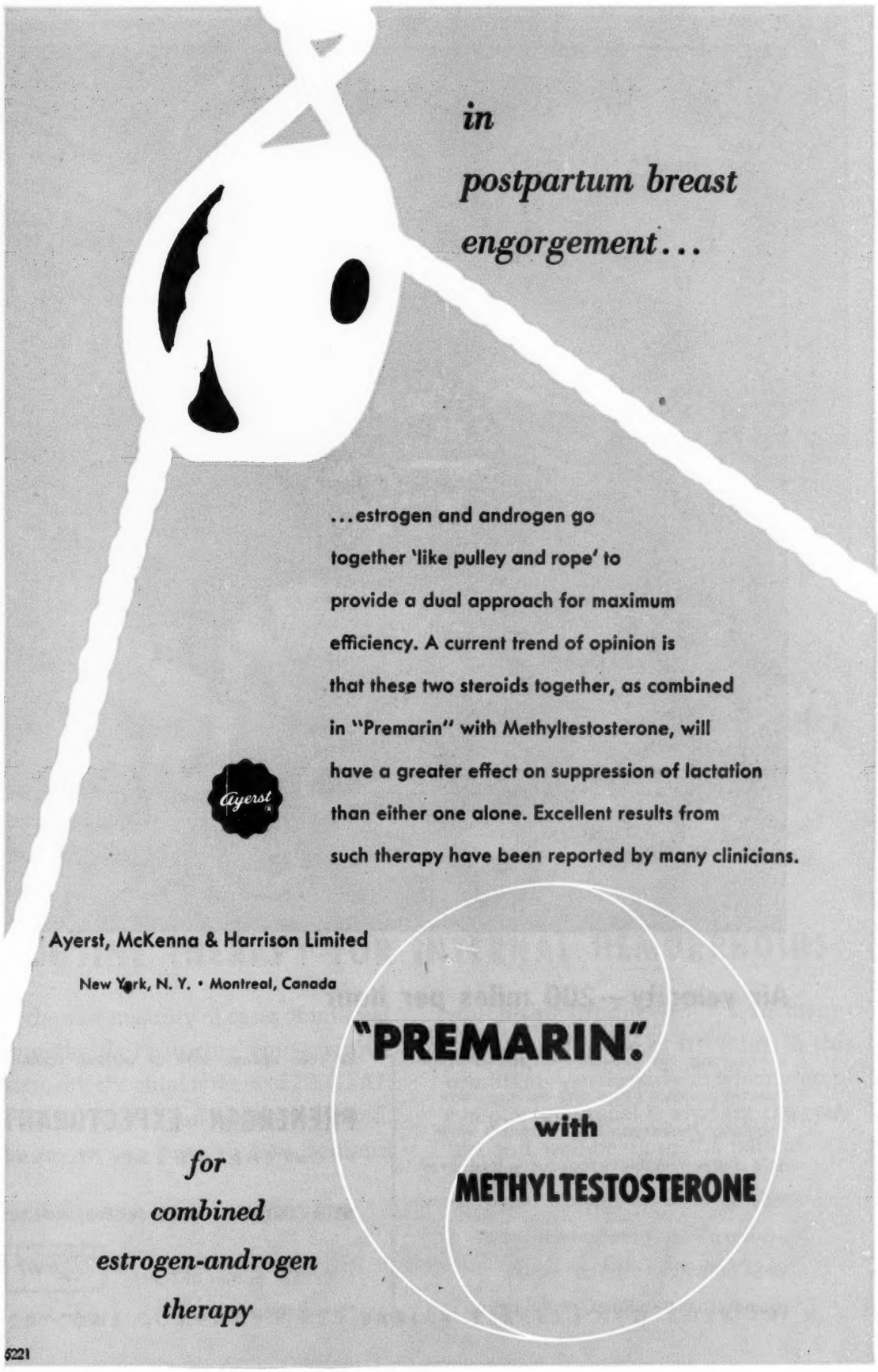
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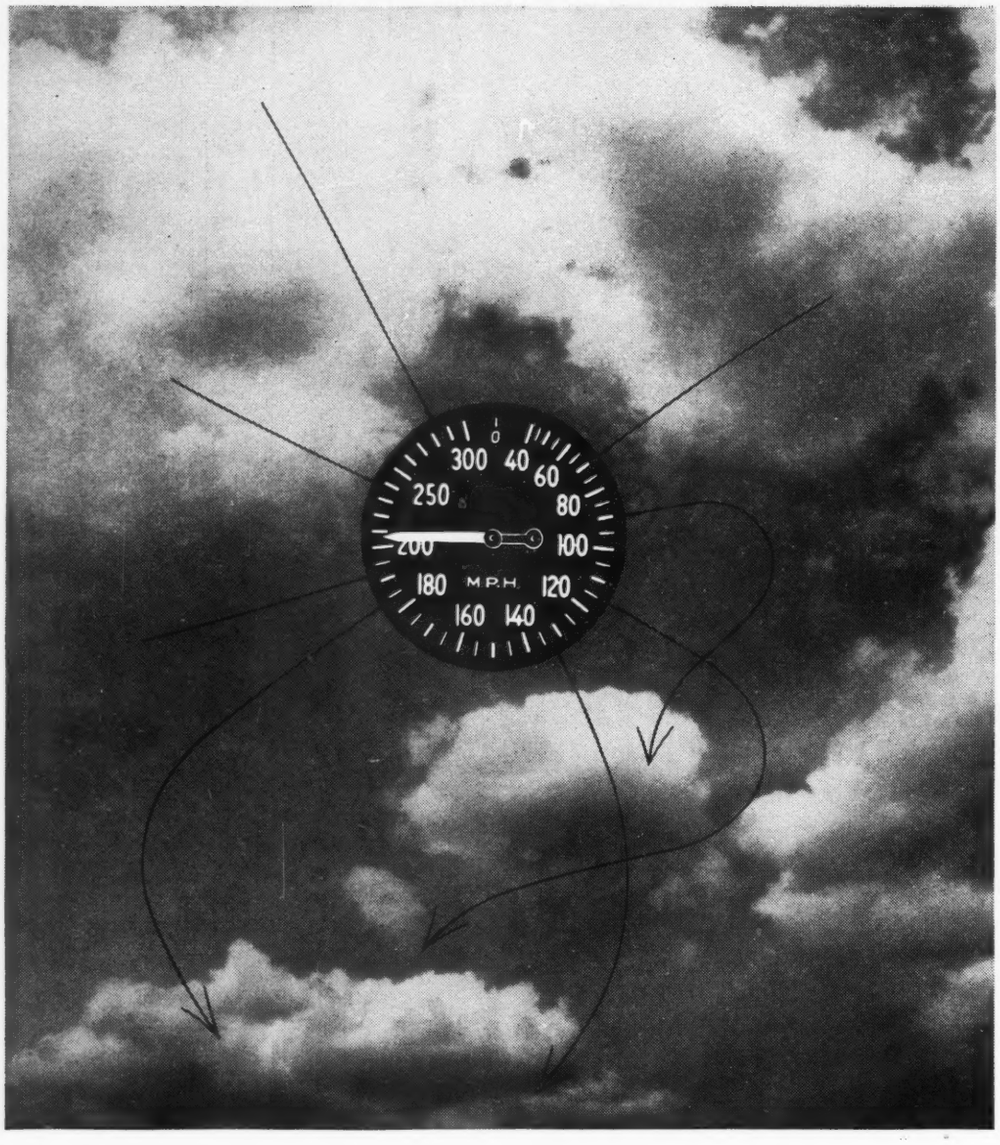

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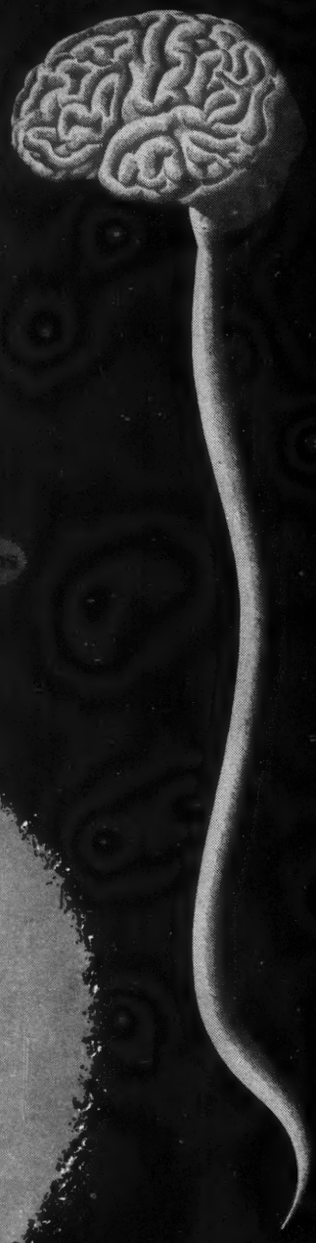

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*Hermann, I. F., and Smith, R. T.: JL.-Lancet 71:271 (July), 1951.

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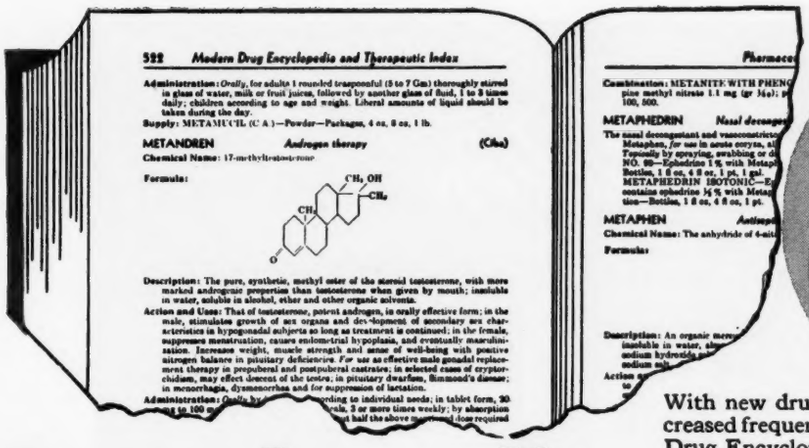

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1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.
2. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.
3. Smith, C. H., and Kunz, H. G.: J. M. Soc. New Jersey *49*:306, 1952.

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Fresh lemon juice, because it is virtually sodium free, is particularly suitable as a seasoning agent in the dietary management of hypertension, cardiac disease, especially when associated with congestive heart failure, and nephritis, and for patients receiving ACTH or cortisone. In weight-reducing diets, when salt restriction is advisable, fresh lemon juice will serve well to make the restricted diet more attractive.

Suggest that a dish of lemon wedges be placed on the table with every meal whenever you have to impose a sodium-low diet.

Sunkist Growers
Los Angeles 54 • California

Sunkist® *Lemons*

"...failure, according to some of the newer evidence...touches off at once a mechanism that hungrily promotes the tubular reabsorption of sodium, just the sort of thing that the mercurials combat so well."*

...and none better than

MERCUHYDRIN®

intramuscularly

subcutaneously or

intravenously

*Beckman, H.: Pharmacology in Clinical Practice. Philadelphia, W. B. Saunders Company. 1957. p. 372.

MERCUHYDRIN

(brand of meralluride, U.S.P.) sodium

Ampuls of 1 cc. and 2 cc. and 10-cc. vials

Leadership in diuretic research

Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

For
the
physician —

...who prefers
penicillin in combination with
other antibacterial drugs:
Gantricillin™ 'Roche' provides
penicillin PLUS Gantrisin® for
wide-spectrum antibacterial therapy.

Combined antibacterial therapy —

...with new Gantricillin™ 'Roche.'

A convenient way of administering 100,000 units of penicillin PLUS 0.5 Gm of Gantrisin®, the more soluble, wide-spectrum sulfonamide, in a single tablet.

WHY TAKE CANDY FROM A BABY?

The overweight patient likes to indulge in sweets. Why not take advantage of this penchant when you prescribe an appetite depressant? ADJUDETS are candy-like troches. They contain d-amphetamine phosphate and essential vitamins, effective aids in reducing regimens Your patient will like this delightfully flavored "sweet." Only 15 calories per troche.

ADJUDETS®

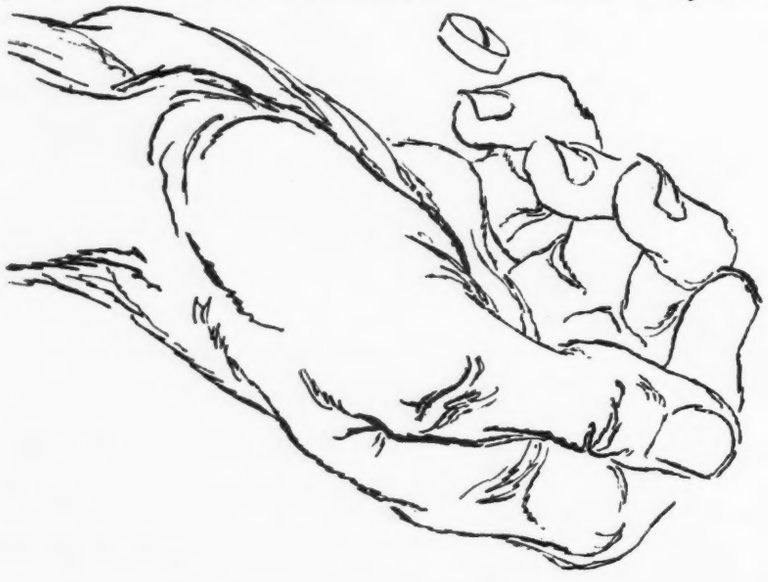
D-AMPHETAMINE-MULTIVITAMIN TROCHES

Supplied: Jars of 36

Wyeth®
Philadelphia 2, Pa.

oral penicillin t.i.d.

. . . for the more common bacterial infectious diseases



Just 1 or 2 Pentids Tablets t.i.d. are particularly effective . . . convenient, easy-to-take . . . cause fewer side effects . . . and are less than ½ the cost of the newer antibiotics.

Bottles of 12 and 100.

formulated for convenient t.i.d. dosage **Pentids**

Squibb 200,000 Unit Penicillin Tablets

SQUIBB

specify Abbott's *new oral antibiotic*

ERYTHROCIN

TRADE MARK

(ERYTHROMYCIN, ABBOTT)

E*specially effective against gram-positive organisms resistant to other antibiotics.*

L*ow toxicity; gastrointestinal disturbances rare; no serious side effects reported.*

S*pecial "high-blood-level" coating.*

Erythrocin, 0.1-Gm. (100-mg.) Tablets, bottle of 25.

INDICATIONS: Pharyngitis, tonsillitis, scarlet fever, erysipelas, pneumococcic pneumonia, osteomyelitis, pyoderma. *Also other organisms* susceptible to its action, which include staphylococci, streptococci, pneumococci. *H. influenzae, H. pertussis,* and corynebacteria.

DOSAGE: Total daily dose of 0.8 to 2 Gm., depending on severity of the infection. A total daily dose of 0.4 Gm. is often adequate in the treatment of pneumococcic pneumonia. *For the average adult* an initial dose of 0.1 to 0.4 Gm. is followed by doses in the same range every four to six hours. *For severely ill patients* doses up to 0.5 Gm. may be repeated at six-hour intervals if necessary. Satisfactory clinical response should appear in 24 to 48 hours if the causative organism is susceptible to ERYTHROCIN. Continue for 48 hours after temperature returns to normal. Abbott

1. McGuire et al. (1952), J. Antibiotics & Chemo., 2:281, June.
2. Heilman et al. (1952), Proc. Staff Meet. Mayo Clin., 27:385, July 16.
3. Haight and Finland (1952), New Eng. J. Med., 247:227, Aug. 14.

Meat...

and the Therapeutic Value of Adequate Protein

Much evidence can be cited in favor of a high protein intake after surgery, trauma, infection, or burns. In supporting the many anabolic and defense mechanisms of the organism in physiologic stress,[1] high-quality protein—such as that of meat—assumes the status of an important therapeutic agent.[2]

Phagocytic activity,[3] formation of antibodies,[4] and rapid healing of wounds[5] are favorably affected by ample protein nutrition. Remission of peptic ulcer,[6] improved resistance to infectious disease,[4] and maintenance of plasma proteins after surgery[7] are other therapeutic effects attributed to an ample protein intake. In the management of ulcerative colitis, protein represents a primary need.[8] Recent advances in the treatment of extensive burns and of hepatic disease emphasize the value of high protein feedings.[9]

These experimental and clinical findings establish the therapeutic value of high protein intake.[10] To assure therapeutic protein adequacy, the dietary should provide a liberal margin of protein over normal requirements.

Meat is an important source of high-quality protein, containing essential as well as nonessential amino acids. In addition, it supplies significant amounts of B group vitamins and of iron, phosphorus, and other needed minerals.

REFERENCES

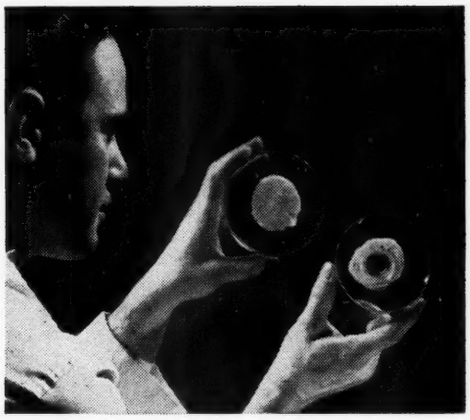
1. Ravdin, I. S., and Gimbel, N. S.: Protein Metabolism in Surgical Patients, J.A.M.A. *144*:979 (Nov. 18) 1950.
2. Mann, G. V., and Stare, F. J.: Nutritional Needs in Illness and Disease, in Handbook of Nutrition, American Medical Association, New York, The Blakiston Company, 1951, chap. 17.
3. Mills, C. A., and Cottingham, E.: Phagocytic Activity as Affected by Protein Intake in Heat and Cold, J. Immunol. *47*:503 (Dec.) 1943.
4. Cannon, P. R.: The Importance of Proteins in Resistance to Infection, J.A.M.A. *128*:360 (June 2) 1945.
5. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, Ann. Surg. *91*:641 (May) 1930.
6. Co Tui, et al.: Hyperalimentation Treatment of Peptic Ulcer with Amino Acids and Dextri-Maltose, Gastroenterology *5*:5 (July) 1945.
7. Lund, C. C., and Levenson, S. M.: Protein in Surgery, J.A.M.A. *128*:95 (May 12) 1945.
8. Welsh, C. S.; Adams, M., and Wakefield, E. G.: Metabolic Studies on Chronic Ulcerative Colitis, J. Clin. Investigation *16*:161 (Jan.) 1937.
9. Cannon, P. R., et al.: Recent Advances in Nutrition with Reference to Protein Metabolism, Lawrence, Kansas, Universlty of Kansas Press, 1950.
10. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, p. 19.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

American Meat Institute

Main Office, Chicago...Members Throughout the United States



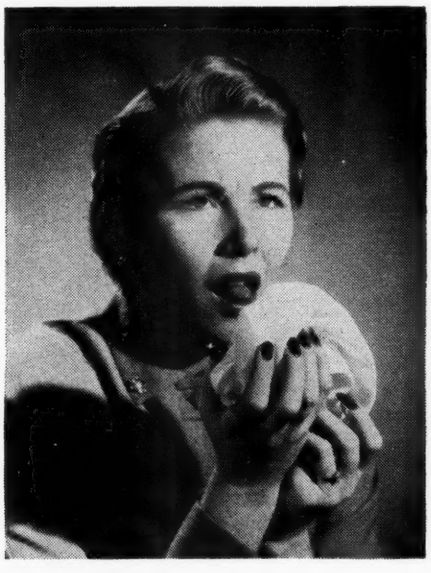
Bacitracin and tyrothricin, as combined in TRACINETS, *are many times more effective in controlling certain infectious organisms* in vitro *than either antibiotic alone.*

TRACINETS *provide local anesthetic action, to give prompt symptomatic relief in both infectious and non-specific sore throat. Each troche contains bacitracin 50 units, tyrothricin 1 mg. and benzocaine 5 mg.*

Antibiotic synergism explains better response obtained in throat infections with

Tracinets®

BACITRACIN-TYROTHRICIN TROCHES



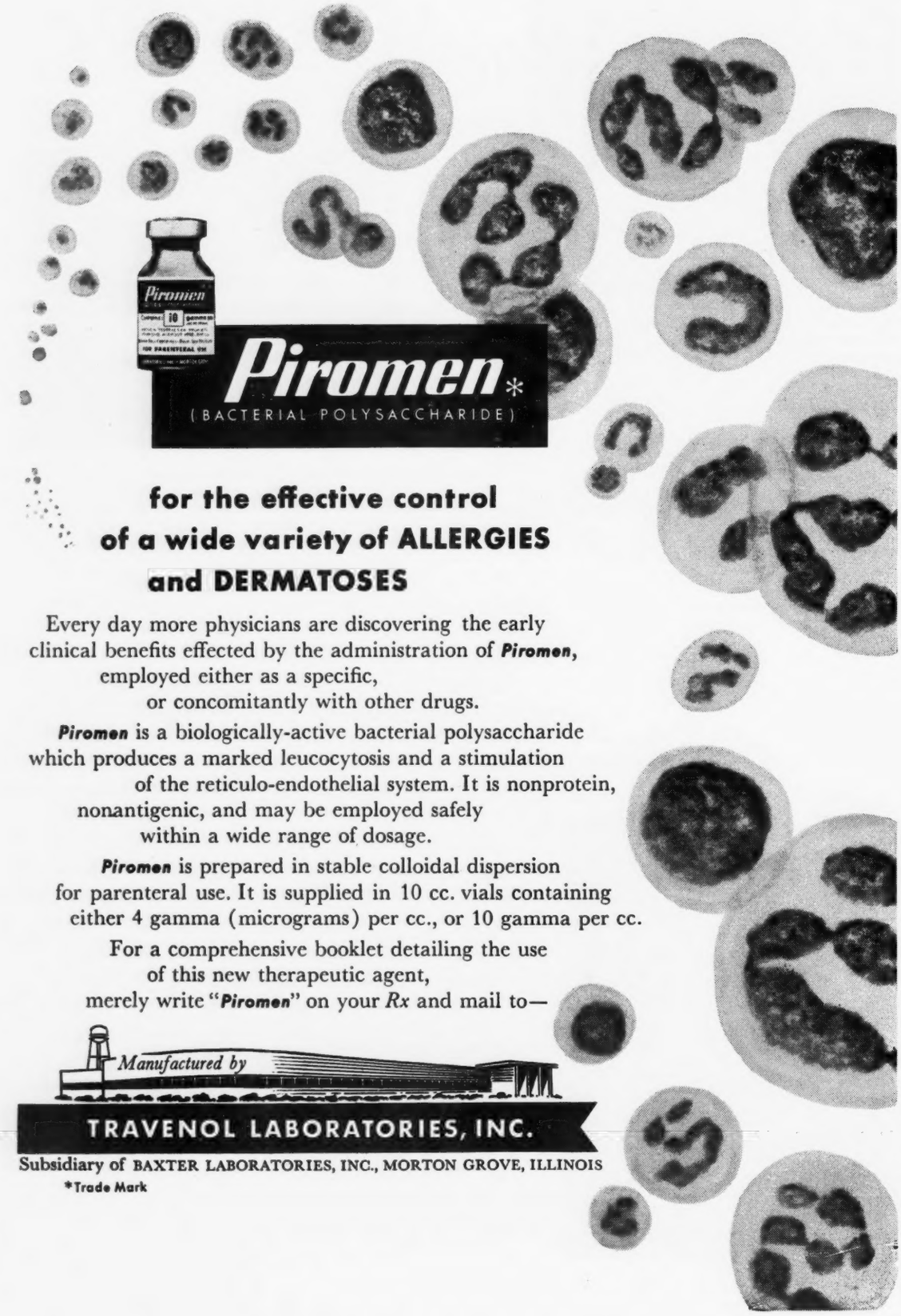
TRACINETS *may be employed to protect against sore throat in the early stages of a cold without danger of sensitizing the patient to antibiotics usually administered systemically.*

Which also contain a local anesthetic for prompt relief of symptoms

SUPPLIED IN PLASTIC VIALS OF 12 TROCHES

Sharp & Dohme

Philadelphia 1, Pa.



Piromen*

(BACTERIAL POLYSACCHARIDE)

for the effective control of a wide variety of ALLERGIES and DERMATOSES

Every day more physicians are discovering the early clinical benefits effected by the administration of ***Piromen***, employed either as a specific, or concomitantly with other drugs.

Piromen is a biologically-active bacterial polysaccharide which produces a marked leucocytosis and a stimulation of the reticulo-endothelial system. It is nonprotein, nonantigenic, and may be employed safely within a wide range of dosage.

Piromen is prepared in stable colloidal dispersion for parenteral use. It is supplied in 10 cc. vials containing either 4 gamma (micrograms) per cc., or 10 gamma per cc.

For a comprehensive booklet detailing the use of this new therapeutic agent, merely write "***Piromen***" on your *Rx* and mail to—

Manufactured by

TRAVENOL LABORATORIES, INC.

Subsidiary of BAXTER LABORATORIES, INC., MORTON GROVE, ILLINOIS

*Trade Mark

Advertisers Index

February, 1953

PHEOCHROMOCYTOMA

causes

one curable form of hypertension

Regitine®

the preferred diagnostic agent

Because of its specificity, this potent adrenergic blocking agent affords an eminently safe, accurate, and simple test for the diagnosis of the hypertension-producing tumor – pheochromocytoma.

When it is left untreated, pheochromocytoma is a progressive and eventually fatal condition. After diagnosis, surgical removal of the tumor effects a complete cure. Therefore, "careful consideration of the possible presence of a pheochromocytoma in every patient with hypertension must now be regarded as a diagnostic obligation."[1] Testing is quickly and simply done with Regitine.

The above chart is a schematic representation of the type of response that you can anticipate in the adult hypertensive patient who does have a pheochromocytoma.

For complete information contact your Ciba Professional Service Representative or write to the Medical Service Division.

REGITINE methanesulfonate (phentolamine methanesulfonate Ciba)
REGITINE hydrochloride (phentolamine hydrochloride Ciba)

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